THE AMERICAN JOURNAL OF PHYSIOLOGY

EDITED FOR

THE AMERICAN PHYSIOLOGICAL SOCIETY

JAN 15 1918
UNIV. OF MICH.
LIBRARY

CONTENTS

PAGE

THE EFFECT OF ORGAN EXTRACTS UPON THE CONTRACTION OF VOLUNTARY MUSCLE. *John Rogers, Helen C. Coombs and Jessie M. Rahe* 97

ADRENALIN VASODILATOR MECHANISMS IN THE CAT AT DIFFERENT AGES. *Frank A. Hartman and Leslie G. Kilborn* 111

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH. XLV. HUNGER, APPETITE AND GASTRIC JUICE SECRETION IN MAN DURING PROLONGED FASTING (FIFTEEN DAYS). *A. J. Carlson* 120

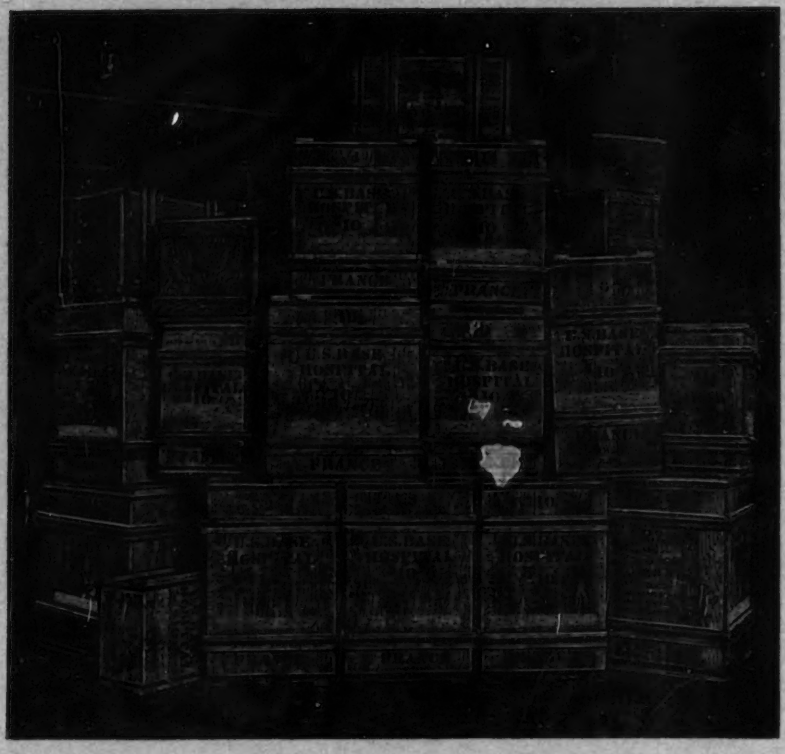
AEQUIRADIO-ACTIVITY. *H. Zwaardemaker* 147

VOL. XLV—No. 2
Issued January 1, 1918

BALTIMORE, U. S. A.
1918

Entered as second class matter, August 18, 1914, at the Post Office at Baltimore, Md., under the act of March 3, 1879

RED CROSS
U. S. ARMY BASE HOSPITAL LABORATORIES



Complete laboratory equipment of Pennsylvania Hospital Unit (U. S. Army Base Hospital No. 10) ready for shipment. European port of destination removed from photograph.

We have supplied the laboratory equipment for twelve hospital units equipped by the American Red Cross and turned over to the U. S. Army as Base Hospitals. This business has involved careful selection of equipment for more or less uncertain conditions of work, and particularly careful packing to meet the requirements of both ocean and inland army transport and service conditions in Europe. We quote the following from a letter received from the Officer in charge of laboratory work in one of the first units sent out:

"American Expeditionary Forces, France,
August 6th, 1917

* * * * *

I want to take this occasion to thank you personally for all the trouble you took to procure our supplies and to have them packed and so carefully labelled as they were (*). We have nothing from any firm which was in any sense comparable to the way your goods were packed—not to mention the clear numbering and addressing of each box, which has saved us untold trouble in locating it and keeping it with us here. * * * "

(*) An itemized typewritten list of the contents of each case was shellacked on the end of each packing case.

The equipment referred to in the above letter was assembled, packed and delivered to an Atlantic port within four days after receipt of order.

ARTHUR H. THOMAS COMPANY

IMPORTERS—DEALERS—EXPORTERS

LABORATORY APPARATUS AND REAGENTS

WEST WASHINGTON SQUARE PHILADELPHIA, U. S. A.

THE AMERICAN
JOURNAL OF PHYSIOLOGY

VOL. 45 JANUARY 1, 1918 No. 2

THE EFFECT OF ORGAN EXTRACTS UPON THE CONTRACTION OF VOLUNTARY MUSCLE

JOHN ROGERS, HELEN C. COOMBS AND JESSIE M. RAHE

From the Johnston Livingston Fund for Experimental Medicine in the Department of Medicine, Cornell University Medical College

Received for publication November 6, 1917

In previous communications in this journal we have attempted to show some of the physiological actions of certain endocrine glands. For this purpose we employed alkaline saline extracts (1) of the pituitary, thyroid, parathyroid, thymus, pancreas, spleen, adrenal, liver and ovary. Such an extract of an organ contains several different materials, each of which has been tested and compared to ascertain, if possible, which portion of the extract is most active. In our experiments, the fresh extract, made with normal salt solution, after straining through gauze and filter paper, has first been treated at room temperature with 10 per cent acetic acid to remove the nucleoproteins. After their separation the clear filtrate has been boiled, filtered and made slightly alkaline with sodium hydroxide; then boiled and filtered again. More or less hydrolysis must therefore occur. The final filtrate represents the non-coagulable part of the original extract and for convenience has been designated as the "residue" of that organ.

The coagulable portion of an organ extract contains, of course, simple proteins such as nucleoproteins, and derived proteins such as acid and alkali albumins, and coagulated proteins. Of these we have tested the nucleoproteins and acid and alkali albumins, and found them to be practically inert except in the case of the pancreas and adrenal (2). The nucleoproteins as well as the "residue" of the pancreas and adrenal glands, show considerable influence upon gastric activity, and in this

respect are exceptional. But the non-coagulable portion of an alkaline saline extract of every organ, on the other hand, (its "residue," as we have designated it), is uniformly active in that it produces certain immediate and characteristic effects. That is, the intravenous injection of each "residue," when the dose is standardized by its nitrogen content, is followed by a quite characteristic fall in blood pressure (3). The "residue" of the adrenal gland alone causes a rise in blood pressure. Each "residue," including those from the pituitary and adrenal glands, produces a more or less characteristic effect upon the contractions of the unstriated muscle fibre of some portion of the intestinal tract (4). When the "residue" stimulates the contractions, the addition of the commercial 1:1000 solution of adrenalin produces an immediate relaxation. Some "residues" increase the flow of pancreatic secretion, while the adrenal "residue" like adrenalin, checks it (5). Others, especially the thyroid "residue," stimulate the amount and acidity of the gastric secretion. The "residue" of the pituitary, as well as of the adrenal gland, inhibits gastric activity (2).

Having previously demonstrated the effect upon unstriated muscle fibre of the intestinal tract, of the "residue" of the endocrine glands, it was thought desirable to study their effect upon striated muscle. The question first arose as to whether the muscle of cats in which the thyroid gland had been removed was more readily fatigable then the normal. A number of cats were accordingly tested with this in view. In several cats the thyroids were removed some days prior to the experiment (care being taken to preserve the parathyroids), and they were allowed to recover from the operation before the experiment was performed. In other cats the glands were removed at the time of the experiment.

In both cases, however, the variation of the limits of the fatigue period were within the limits of variation of the normal cat. This is what one would expect since it has been shown that when the parathyroids remain intact, thyroidectomized animals may live for a long period without exhibiting any abnormal symptoms (6).

The general effect of thyroidectomy on the fatigability of the organism, the parathyroids remaining intact, was also studied in another manner. A number of cats were thyroidectomized and after their necks were healed, or in about two weeks, they were made to run in an electrically turned (wheel) treadmill until they were fatigued. A corresponding number of normal cats were run under the same conditions as controls. There was, of course, considerable variation in the period before the onset of fatigue, depending upon the age and size of the animal,

but within allowable limits of variation there was no appreciable difference between the normal cats and those in which the thyroids had been removed.

Following is a typical protocol of such an experiment, June 13, 1917.

Female cat, (operated on, thyroids removed, parathyroids intact, May 29.)
10.45 a. m. Placed in wheel; wheel started revolving.
11.25 a. m. Cat fatigued so that it slid in wheel instead of running.
11.40 a. m. Normal female cat placed in wheel; wheel started revolving.
12.28 p. m. Cat fatigued so that it slid in wheel instead of running.

Such finding corroborates the other experimental data. Apparently within such a period of time a sufficient amount of the thyroid "hormone" still remains in the circulation to be effective, or some other mechanism is finally able to bring about a compensation. Whether this compensation is permanent is, of course, another question. The time factor is probably an important element here but experimentation has not yet been carried out as to the ultimate effects of thyroidectomy on striated muscle.

After it had been ascertained that the fatigability of the muscle was apparently not influenced by more or less immediate thyroidectomy, the effect of the intravenous injections of various extracts upon the contraction of partially fatigued muscle was studied.

Normal adult cats were etherized, then tracheotomized and etherization continued through a tracheal cannula. The rectus abdominis muscle of one side was then freed from its attachment to the ribs and fastened at the upper end to a writing lever by means of a series of pulleys. As the portion of the rectus abdominis below the ribs was undisturbed, the blood and nerve supply remained fairly intact. One electrode from the induction coil was attached to the free end of the muscle and the other to the muscle near the pubic symphysis. The entire muscle was thus stimulated from a storage battery through an induction coil at the rate of one shock a second, on the break only, with a current of 0.7 amperes. An ammeter indicated that the stimulus was constant. The diminishing excursions of the writing lever in response to the same stimulus indicated the increasing fatigue of the muscle.

The dosage of each extract was measured by its nitrogen content calculated as protein so that the standard dose contained 0.1 gram protein. Blood pressure from the carotid artery was taken at the same time that the effect of intravenous injection upon the muscle was studied. When the excursions of the writing lever had decreased to a magnitude of less

than one-half of their original height, a standard injection of a thyroid preparation was given by the femoral vein. The following materials obtained from the fresh thyroid gland were tested in these experiments: The non-coagulable "residue" of the alkaline saline extract; nucleoproteins; coagulable proteins; Kendall's so-called "active principle" (7); a thyroid extract prepared according to Eddy's method for pancreas-vitamines (8); a "residue" made from commercial desiccated thyroid powder; and finally "residues" made from diseased human thyroids. These were obtained at operations and were of two kinds: *a*, consisting of simple goitre tissue removed from patients who gave no evidence of hypo- or hyperthyroidism; *b*, consisting of diseased thyroid tissue excised from patients who presented marked evidences of hyperthyroidism or expothalmic goitre.

Following is a typical protocol of the way in which the action of the glands was studied. The effects of a single organ extract were first observed, and it was then found that the action of several extracts could be studied without any complication in the effect upon the muscle or the blood pressure. The combinations in which the extracts were given were numerous. No set rule as to order was followed, in order that any deviation in results might be more readily checked up.

Protocol of July 23, 1917. Male cat, ether, tracheotomy

10.15 a. m. Femoral vein exposed for injection.

10.35 a. m. Blood pressure apparatus set up, with cannula in left carotid. Normal blood pressure taken.

10.55 a. m. Left rectus abdominis attached to pulleys, electrodes fastened and stimulation begun.

11.20 a. m. 3 cc. thyroid residue injected in femoral vein. Note fall in blood pressure, lasting two minutes. Note increase in muscle contractions.

11.40 a. m. 2.8 cc. alcoholic thyroid extract (95 per cent) injected. Note fall in blood pressure and lack of effect on muscle.

11.55 a. m. 4 cc. simple goitre residue injected. Note very slight fall in blood pressure and lack of effect on muscle.

12.15 p. m. Trachea occluded. Cat dies.

Of all these extracts, the non-coagulable "residue" of the alkaline saline extract, made from fresh thyroid glands, was found to be most effective in reënergizing fatigued voluntary muscle (fig. 1). The "residue" made from commercial desiccated thyroid powder showed only a fraction of the activity of the "residue" made from fresh glands (fig. 2). None of the other "extracts" or preparations mentioned above, including those from diseased thyroids, had any effect upon voluntary muscle, although it is interesting to note that the 95 per cent alcoholic thyroid extract is a greater stimulant of gastric secretion than the "residue" of

the alkaline saline extract which is so potent for striped muscle—a point which is at present being studied in a research to be published later.

It might have been expected that that "residue" would be inert which was made from the simple adenomata, or cyst-adenomata, of thyroids which in life gave no constitutional symptoms. Tumors of secreting structures are not generally believed to produce any active material. But that a "residue" of true hyperthyroid tissue should also be inert is somewhat surprising. The thyroid gland of exophthalmic goitre ap-

Fig. 1. The failing contraction of the fatigued muscle is shown at the left. At the point on the left indicated by the cross, 5 cc. of thyroid "residue" containing 0.1 gram of protein was injected. The succeeding increased excursions of the writing lever show the effect of the injection upon the previously fatigued muscle.

parently produces too much secretion. Is it possible that this excessive product is of extremely poor quality?

A study of the blood pressure tracings brings out another interesting variation. Organ extracts, with the exception of those from the adrenal gland are almost uniformly vaso-depressor. As may be seen from the tracings (fig. 3), blood pressure falls immediately on injection of the thyroid "residue," then rises again to the normal level within a short time

or from two to five minutes. The thyroid extract prepared according to Eddy's method for pancreas-vitamines, however, appears to have a pressor effect. Blood pressure rises and remains up for from five to seven minutes after injection, before it descends to the normal level again (fig. 4). The curve which it presents is very similar to the blood

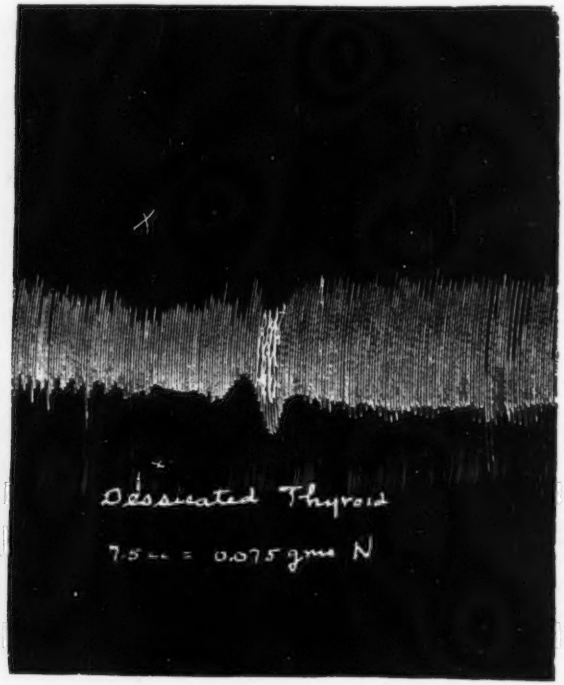


Fig. 2. On the left is shown the decreasing contractions of the muscle in the process of fatigue. On the right is shown the slight invigoration produced by the injection of a "residue" made from commercial desiccated thyroid.

pressure curve shown after intravenous injection of adrenalin or the adrenal residue (figs. 5 and 6).

Clinically, one of us (J. R.) has observed several cases of hyperthyroidism with high blood pressure in which the blood pressure fell to normal immediately or very soon after the enucleation of one or more encapsulated tumors of the thyroid. This experience, in conjunction

with the pressor effect of the thyroid "vitamine," (?) suggests that the pathological tissue excised from patients with high blood pressure may secrete a similar toxic substance.

After ascertaining that our thyroid "residue" was the only thyroid preparation which was capable of energizing fatigued muscle, we have

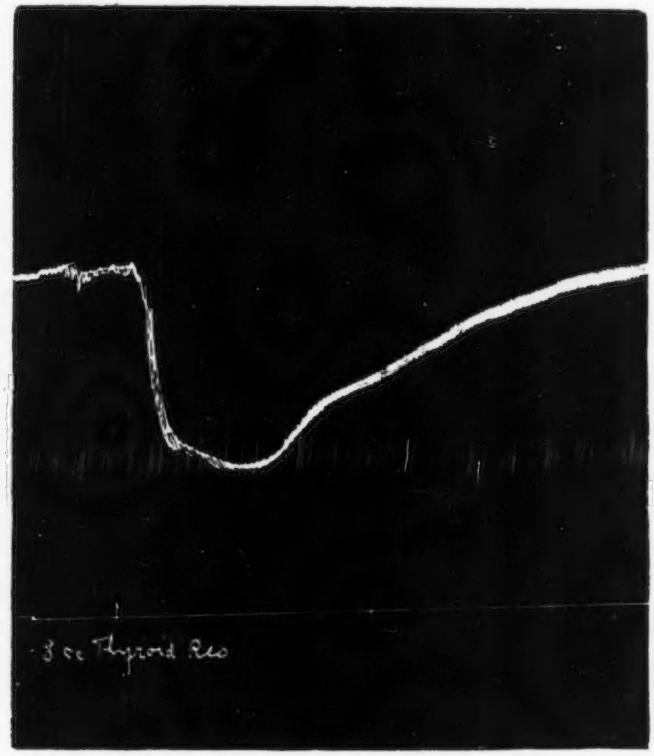


Fig. 3. This shows the characteristic fall in blood pressure which is produced by the intravenous injection of the thyroid residue.

similarly tested corresponding materials derived from the other endocrine glands including liver, spleen, ovary and pancreas. We have found that the "residues" of the parathyroid (fig. 7) and the adrenal gland (fig. 8) and also the commercial 1 : 1000 solution of adrenalin (fig. 9)

show a power like that of the thyroid, or reënergizing fatigued muscle. No other materials or extracts obtained from these or other organs exhibited any of this kind of activity.

The thyroid, parathyroid and adrenal glands alone seem capable of invigorating fatigued muscle. It should be noted here that our adrenal

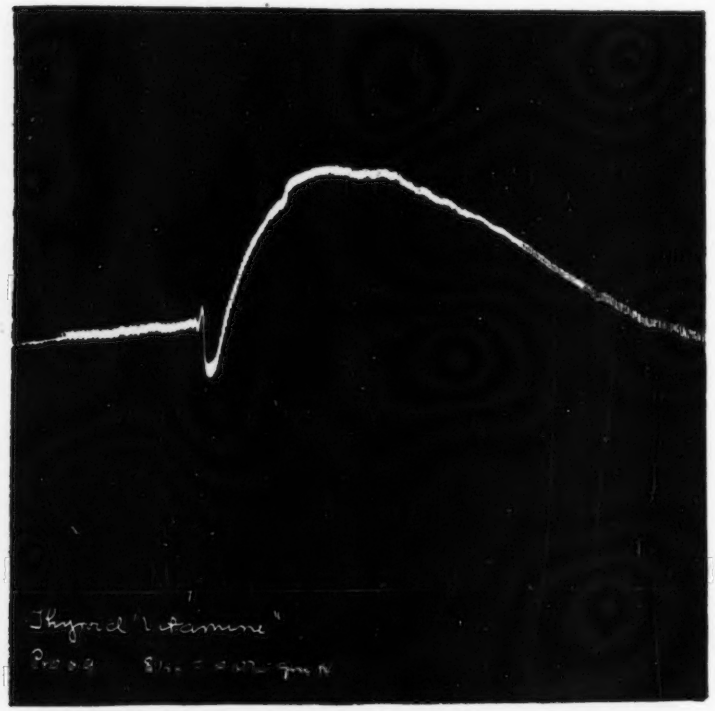


Fig. 4. This shows the rise in blood pressure produced by the intravenous injection of the thyroid "vitamine" (?) It is preceded by a slight initial fall in pressure.

"residue" responds to the tests for adrenalin but apparently contains some other active material. Our "residue" is derived from the whole gland, while adrenalin or adrenin is obtained only from the medulla. Nevertheless, when the adrenin doses of the adrenal "residue" and of the 1:1000 adrenalin solution are the same, the effects correspond.

This, however, does not necessarily indicate that our adrenal residue is the exact physiological equivalent of adrenalin.

The next question concerns the mechanism or manner in which the thyroid, parathyroid and adrenal glands act upon the voluntary muscles. If, in the experimental animal, the spinal roots of the last six dorsal and all five lumbar nerves are sectioned on the side on which the rectus abdominis is being stimulated, fatigue of the muscle takes place somewhat more rapidly than in the normal or thyroidectomized animal.

Fig. 5. This shows the effect upon the blood pressure tracing of the injection of the commercial 1: 1000 solution of adrenalin.

This may be due either to the general exhaustion produced by the rather severe operation, or to lack of control of the peripheral by the central nervous system, or to both influences.

After section of the spinal roots of the nerves which supply the rectus abdominis muscle, however, the effects upon the fatigued muscle of the intravenous injection of the extracts is the same as in the muscle with the nerve supply intact. The point of action of the gland extracts must, therefore, be near the muscle fibre itself. Gruber (9) has demonstrated

in the case of adrenalin that the threshold stimulus of a denervated muscle was unaffected by curare and that adrenalin had no effect upon the curare threshold in this muscle.

The threshold of a curarized muscle with the nerve intact, however, is affected by fatigue which adrenalin counteracts. If curare acts upon Langley's "receptive substance" (10) between the nerve endings and the muscle, fatigue and adrenalin [as well as our "residues"] must act at another point nearer the muscle than the "receptive substance."

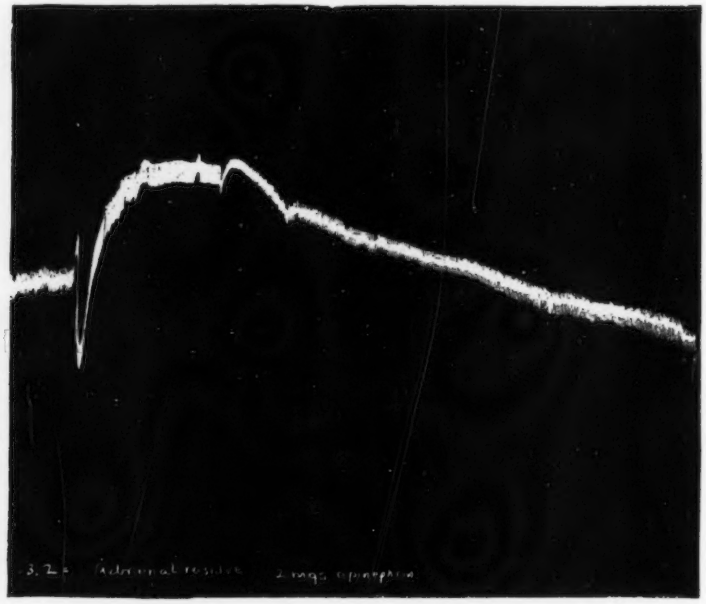


Fig. 6. This shows the effect upon the blood pressure tracing of the intravenous injection of an amount of adrenal residue which contained the same quantity of adrenalin as was given in figure 5.

In these experiments we have endeavored to demonstrate that materials derived from the thyroid, parathyroid and adrenal glands, and from those endocrine glands only, have a direct influence upon the contraction and fatigue of voluntary muscles. We have further sought to determine chemically the general group of substances in which the active principle of these endocrine glands is to be found. Such work must, however, at this stage be regarded as purely suggestive, since it calls

for a very thorough working out from physiological, chemical and clinical viewpoints.

Tests made with the various materials derived from the thyroid, parathyroid and adrenal glands show that fatigued muscle can best be invigorated by the non-coagulable or "residue" portion of an alkaline saline extract of each organ. This "residue," it should be noted, con-

Fig. 7. This tracing shows the effect upon the failing contraction of fatigued voluntary muscle of the injection of the parathyroid "residue." 4. cc. = 0.1 gram of protein.

tains slightly hydrolized material, and in our experiments has always been made from "fresh" glands. A "residue" of desiccated commercial thyroid material is not nearly so active as extracts made from the fresh gland and, therefore, the usual thyroid medicament must be more or less unsatisfactory.

Muscular weakness is quite evident in the clinical condition commonly

described as that of hypothyroidism. Hypofunctionation of endocrine organs other than the thyroid and the adrenal is not so well recognized but, as a rule, seems also to be accompanied or manifested by asthenia; that is, muscular weakness is a constant and striking symptom not only in hypothyroidism and hypoadrenalism (Addison's disease) but also seems to occur in many other analogous conditions.

Fig. 8. This tracing shows the effect upon the failing contraction of fatigued muscle of the intravenous injection of the adrenal "residue." The 4 cc. contained approximately the same amount of adrenalin as the 3 cc. of adrenalin 1:1000 shown in figure 9.

From our experiments we infer that the thyroid gland, through its secretion, affects the neuro-muscular junction and thus in some unknown manner invigorates muscular contractions. It is, therefore, reasonable to suppose that the marked muscular weakness of hypothyroidism, at least in part, is due to the deficiency of thyroid secretion and consequent absence of the usual neuro-muscular activation or stimulus. This as-

thenia of hypothyroidism can generally be relieved by thyroid feeding, which usually means the administration by mouth of small amounts of the desiccated gland. It is scarcely conceivable, however, that digestion of this material can result in the introduction into the circulation of a substance which is so closely equivalent to the thyroid product as to act directly upon the neuro-muscular apparatus or junction as our

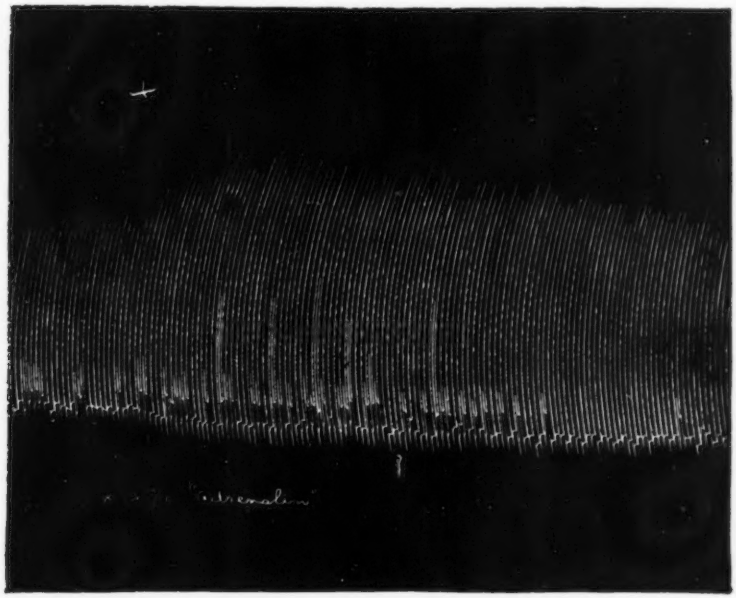


Fig. 9. This tracing shows the effect upon the failing contraction of fatigued muscle of the intravenous injection of 3 cc. of the commercial 1:1000 solution of adrenalin.

thyroid "residue" apparently does. In hyperthyroid conditions there is the same or a worse asthenia, and it is generally intensified by thyroid feeding. According to our tests, the extract of the hyperthyroid gland is entirely inert. Consequently, the usual muscular weakness which is present in these conditions appears to be virtually that of hypothyroidism. There are undoubtedly some cases of hyperthyroidism in which all the symptoms, including the muscular weakness, can be relieved and not intensified by thyroid feeding. Nevertheless, these cases are

exceptional. One can only conjecture the meaning of these apparent contradictions. In the absence of thyroid secretion, or in the presence of a very poor quality of secretion, there should, according to our experiments, be a deficiency in the muscular energy. More than this is unknown.

CONCLUSIONS

1. Intravenous injection of the non-coagulable portions of the alkaline saline extracts of the thyroid, parathyroid and adrenal glands increase the vigor of contraction of fatigued voluntary muscle.

2. The commercial 1 : 1000 solution of adrenalin shows a similar stimulant effect.

3. No other materials tested, derived from the thyroid, parathyroid and adrenal glands show any stimulant effect upon fatigued voluntary muscle.

4. Materials from the other endocrine glands show no effect upon voluntary muscle contraction.

5. Desiccation of the thyroid gland appears to lessen or destroy its activity.

6. Excision of the thyroid appears to have no immediate effect upon the fatigability of voluntary muscle.

7. "Residues" made from adenomatous or cyst-adenomatous thyroid material, as well as those made from the supposedly overactive gland of hyperthyroidism, are inert.

BIBLIOGRAPHY

(1) FAWCETT, ROGERS, RAHE AND BEEBE: This Journal, 1915, xxxvi, 113.
(2) ROGERS, RAHE, FAWCETT AND HACKETT: This Journal, 1916, xxxix, 345.
(3) FAWCETT, ROGERS, RAHE AND BEEBE: This Journal, 1915, xxxvii, 453.
(4) FAWCETT, RAHE, HACKETT AND ROGERS: This Journal, 1915, xxxix, 154.
(5) ROGERS, RAHE, FAWCETT AND HACKETT: This Journal, 1916, xl, 12.
(6) MATHEWS: Physiological chemistry, 1916, 675.
(7) KENDALL: Journ. Biol. Chem., 1915, xx, 501.
(8) EDDY: Journ. Biol. Chem., 1916, xxvii, 116.
(9) GRUBER: This Journal, 1917, xliii, 530.
(10) LANGLEY: Journ. Physiol., 1907, xxxvi, 348.

ADRENALIN VASODILATOR MECHANISMS IN THE CAT AT DIFFERENT AGES

FRANK A. HARTMAN AND LESLIE G. KILBORN

From the Department of Physiology, University of Toronto

Received for publication November 13, 1917

It has been established by a number of investigators (1), (2) that in the cat the normal response of the vascular system to small doses of adrenalin is such as to cause a fall in blood pressure. This effect is accomplished by a dilatation in the blood vessels in the muscles (3). Moreover the dilatation is controlled by a central nervous mechanism (4).

We accidentally discovered that adrenalin fails to produce a fall in blood pressure in young kittens with any dose, however small. The only reaction given is a rise. Inasmuch as the fall in blood pressure is controlled by a central nervous mechanism it seemed possible that the failure of this mechanism to develop at an early age might account for the reaction in young kittens.

With the hope of throwing more light on the nature of the adrenalin vasodilator mechanism we have made a study of cats at different ages.

The methods employed in this research were similar to those used in previous researches (4) but with the following modifications: Much smaller bellows than those used in adult cats were found advantageous in registering volume changes of the limb or intestine of kittens. Bellows with a base 26 mm. by 13 mm. were used in a majority of the experiments, while occasionally in the youngest kittens a smaller bellows with a base 17 mm. by 10 mm. was tried. All animals were under the influence of ether.

When the age of the kittens was unknown, it was necessary to make an estimate from the animal's weight. These estimates were based upon the weights of five kittens, whose ages were known, ranging from 0.3 kgm. to 1.3 kgm. in weight. The ages so determined are close enough for our purpose because the earliest occurrence of the adrenalin vasodilator mechanism is unquestionably variable.

BLOOD PRESSURE REACTION AT DIFFERENT AGES

A study of the blood pressure responses might be expected to give us an idea of the age at which the adrenalin vasodilator mechanism begins to appear. We therefore sought to answer our problem by means of the blood pressure reaction.

The youngest kittens employed were of known age (three weeks) and weighed 0.3 kgm. and 0.32 kgm. respectively. The threshold for blood pressure response to adrenalin was high in both cases. In the first, 0.1 cc., 1:100,000 caused a rise from 46 mm. to 49 mm., while less than that produced no effect. Even larger doses produced a smaller percentage rise than that from proportional doses in older kittens, although the duration of the effect might be as long (see *a*, fig. 1).

Eight older kittens weighing from 0.6 kgm. to 0.67 kgm. (about eight weeks of age) possessed a lower threshold for adrenalin, in some instances being as low as 0.2 cc., 1:1,000,000. In only two of these animals was there an occasional fall of blood pressure succeeding the rise. When it did occur it was small in amount. A depressor effect at this age was exceptional (see *b*, fig. 1). Kittens even older failed to give a fall in blood pressure with adrenalin. Seven individuals weighing respectively 0.72 kgm., 0.75 kgm., 0.9 kgm., 0.9 kgm., 0.95 kgm. and 1.05 kgm. (estimated ages, nine to eleven weeks), gave a rise without a fall in every injection, however small.

On the other hand animals weighing 1 kgm. or more usually gave a rise and fall in blood pressure with small doses, although repeated injections in the same animal might not always do so (*c* and *d*, fig. 1). It might be suggested that the failure of a depressor reaction in these cases was due to the easy fatigue of an incompletely developed mechanism. Kittens of the following weights gave the depressor reaction: 1.0 kgm., 1.0 kgm., 1.1 kgm., 1.3 kgm.

As the animals became older the pressor effects from small doses of adrenalin became gradually less and less while the fall in blood pressure became greater and more prolonged. Finally in the adult animal the rise became insignificant or in some cases a pure fall resulted (see fig. 1).

A study of the blood pressure reaction has shown that the depressor response to adrenalin begins to appear at the age of eleven or twelve weeks. From that age onward the depressor response encroaches more and more upon the pressor effect until finally the latter may almost disappear, provided small doses of adrenalin are injected. This graded increase of the depressor response with the growth of the animal indicates a gradual development of the adrenalin vasodilator mechanism.

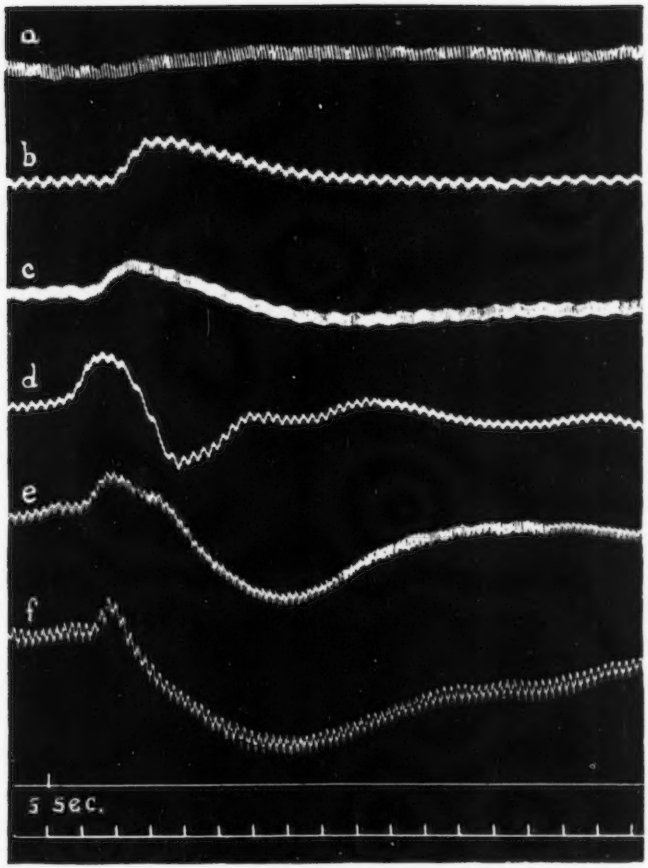


Fig. 1. Different types of blood pressure curves produced by adrenalin in cats of different ages.

	WEIGHT	AGE	DOSE OF 1: 100,000 ADRENALIN	INITIAL HEIGHT OF BLOOD PRESSURE
	kgms.	*weeks*	*cc. per kgm. of body weight*	*mm. of mercury*
a	0.30	3	1.67	60
b	0.62	8	0.16	67
c	1.0	11	0.20	119
d	1.3	14	0.076	170
e	1.8	24	0.17	150
f	2.8	adult	0.071	151

It seemed at first that we had settled the question as to the age at which the adrenalin vasodilator mechanism first appears by a study of the blood pressure reaction. But in work on adult cats, which is to be published soon, we found later that an adrenalin vasodilator mechanism might be acting in an animal although the blood pressure response was a rise. Therefore without a study of the volume changes in the organ concerned, we cannot be certain of our solution.

For reasons given in another research (4, p. 366) we are led to treat separately the adrenalin vasodilator mechanism for the limb and the intestinal adrenalin vasodilator mechanism. It might be well to briefly repeat those reasons. First, there is a difference of threshold, i.e., the mechanism for the intestine has a higher threshold on the aver-

Fig. 2. Effect of 0.4 cc. adrenalin, 1:100,000 on the volume of the intestine and hind limb in a kitten three weeks old (0.32 kgm.). Smaller doses produced similar though less marked effects. (Reduced ½.)

age than that for the limb. Second, a difference in reversal, i.e., no increase in the dose of adrenalin ever changes intestinal dilatation to constriction when once the dilatation threshold is passed, while such an increase does cause a reversal from dilatation to constriction in the limb. These observations suggest different types of mechanisms. We will therefore discuss them separately.

THE ADRENALIN VASODILATOR MECHANISM FOR THE LIMB

Although we have employed the hind limb in this study, there is ground for assuming that its reaction (provided skin effects are negligible) represents the reaction for the skeletal muscle throughout the organism. We have therefore considered active adrenalin dilatation of the hind limb as proof of the presence of the adrenalin vasodilator mechanism for skeletal muscle.

We have sought for the presence of this mechanism in nine kittens at varying ages. The smallest to give undoubted evidence of its existence was nine or ten weeks old (0.85 kgm.) (see fig. 3). However the repeated injections of similar doses did not always produce active dilatation. This finding is parallel to the observation on the inconstancy of the depressor response in blood pressure in kittens first to show the reaction. Five younger kittens from three to eight weeks old gave no active dilatation of the limb. (See fig. 2.)

Two kittens about eleven weeks old (1 kgm.) reacted by limb dilatation more easily than did the nine-weeks-old kitten. As the animals

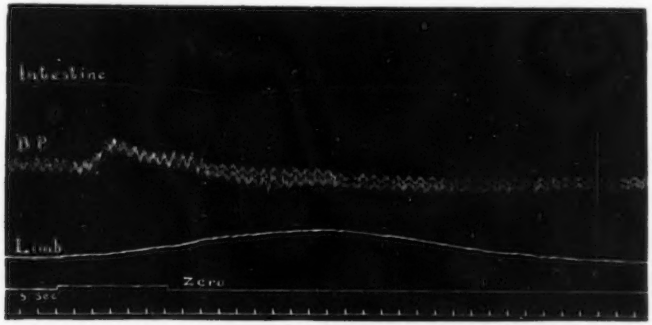


Fig. 3. Active vasodilatation in the limb of a kitten about nine weeks old (0.85 kgm.). Dose of adrenalin 1 cc., 1:100,000. (Reduced ½.)

grew older the reaction was elicited with greater constancy. At six months the response resembled more that of the adult.

In general we may say that the limb mechanism begins to function at or possibly before the eleventh week. Inasmuch as the fall in blood pressure is due to the action of an adrenalin vasodilator mechanism for skeletal muscle, we should find that the depressor response of blood pressure and the active limb dilatation begin to appear at the same age. Within the limit of experimental conditions we have found this to be true.

THE INTESTINAL VASODILATOR MECHANISM

Although the intestinal vasodilatation from adrenalin may contribute to the fall in blood pressure with doses that do not produce constriction in skeletal muscle, as soon as these doses are exceeded, intestinal vasodilatation merely subtracts from the pressor effects of the con-

stricting skeletal muscle. Therefore we cannot expect to throw much light on the blood pressure reaction by a study of the development of this mechanism. But because it seems to be of a different type we were anxious to compare its development with that of the limb mechanism.

Fig. 4. Intestinal reaction to a large dose of adrenalin, 0.4 cc., 1:20,000 in a three-weeks-old kitten (0.32 kgm.). (Reduced ½.)

The volume changes in the intestine, resulting from the injection of adrenalin into the general blood stream, were observed in eleven kittens ranging in age from three weeks to six months. The amounts of adrenali ninjected varied from that just sufficient to give a response to massive doses. The absence of the intestinal adrenalin vasodilator mechanism was considered proven if massive doses failed to cause dilatation.

All kittens up to about eleven weeks of age (eight) failed to show the presence of an adrenalin vasodilator mechanism for the intestine. Three of about this age showed nothing but constriction, while a fourth gave a marked dilatation (see fig. 6). The character of the constriction differed somewhat with the age of the animal, younger kittens showing a more prolonged effect than older kittens (see figs. 4 and 5). This might be due to the vasodilator effects beginning to appear in the older kittens because we know that in adults the constriction is cut short by dilatation. At that stage the vasodilator mechanism is fully developed.

On account of differences already mentioned we have been led to consider the adrenalin vasodilator

mechanisms as of two different types. If this is true, the question arises as to whether the limb and intestinal adrenalin vasodilator mechanisms begin to function at the same age. This could best be answered by seeking for them in the same individual. Ten kittens were tested for the presence of both the limb and intestinal adrenalin vasodilator mechanisms. The youngest to show the presence of either mechanism was about nine weeks old. There was positive evidence of the presence of the adrenalin vasodilator mechanism for the limb, but absolutely no trace of the other mechanism. Two kittens about

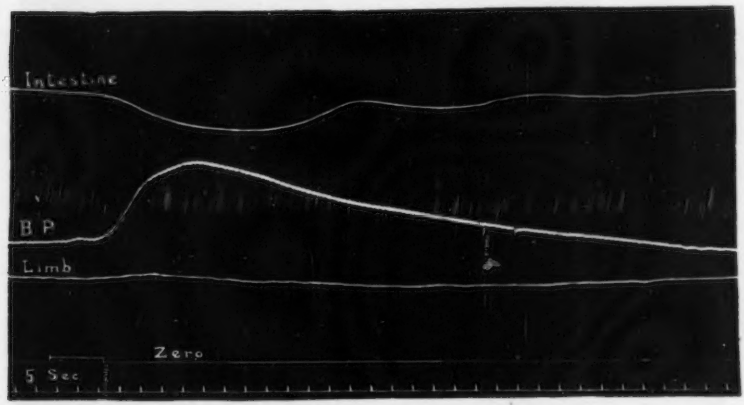


Fig. 5. Less prolonged intestinal constriction from a large dose of adrenalin (0.5 cc., 1:10,000) in an older kitten than in the previous figure. Age eight weeks, weight 0.67 kgm. (Reduced ½.)

eleven weeks of age gave active limb dilatation with adrenalin but absolutely no intestinal dilatation. We may conclude from these results that the two mechanisms may begin to function at different ages in the same individual. Moreover in every case so far noted (three) the adrenalin vasodilator mechanism for the limb functioned earliest. These observations lend support to the idea that the two mechanisms are of different types.

In conclusion we may ask: Why do the adrenalin vasodilator mechanisms develop so late in the life of the individual? Does it mean that the mechanism is one of the last to appear in the evolution of the cat? If so, it might be that they are specialized mechanisms occurring

Fig. 6. The youngest kitten to give evidence of the presence of the intestinal adrenalin vasodilator mechanism. Age, eleven to twelve weeks. Weight, 1.1 kgm. Adrenalin injected, 0.5 cc., 1:10,000. (Reduced ⅔.)

only in the carnivora. (Their presence has been proven in the dog.) A systematic survey of the vertebrates for the presence of these mechanisms is in progress in this laboratory.

SUMMARY

1. The smallest effective doses of adrenalin produce only a rise in blood pressure in young kittens.

2. The threshold for adrenalin blood pressure effects is high in young kittens, decreasing as they grow older.

3. The response to adrenalin of a fall in blood pressure begins to appear at about eleven weeks.

4. The increasing of the depressor effects from the slight fall succeeding a rise in younger animals to a marked almost pure fall in adults indicates a gradual development of the adrenalin vasodilator mechanism.

5. This fall in blood pressure seems to be due to vasodilatation in skeletal muscle, for the two begin to appear simultaneously in most instances.

6. The intestinal adrenalin vasodilator mechanism often develops later than the adrenalin vasodilator mechanism for the limb. This supports the view that the two mechanisms are of different types.

BIBLIOGRAPHY

(1) Cannon and Lyman: This Journal, 1913, xxxi, 376.
(2) Hartman: Ibid., 1915, xxxviii, 438.
(3) Hoskins, Gunning and Berry: Ibid., 1916, xli, 513.
(4) Hartman and Fraser: Ibid., 1917, xliv, 354.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XLV. Hunger, Appetite and Gastric Juice Secretion in Man During Prolonged Fasting (Fifteen Days)

A. J. CARLSON

From the Hull Physiological Laboratory of the University of Chicago

Received for publication November 15, 1917

There are two phases of the physiology of prolonged fasting that require further investigation on man, namely *a, the hunger mechanism and the hunger sense,* and *b, the gastric juice secretion.*

The reliable literature on prolonged fasting in man is practically unanimous on the point that the fasting person feels little or no hunger after the first three or four days. In the thirty-one days' fast of Levanzin, carried out in the Nutrition Laboratory of Carnegie Institution in 1912, the subject claimed he felt no hunger at any time (3). The observations of Boldireff (4) on fasting dogs appear to support these reports on man. It is now established that the sensation of hunger is induced by a certain type of tonic and peristaltic contractions of the empty or nearly empty stomach (1), (2). Boldireff concluded that the stomachs of fasting dogs become atonic and quiescent after the third or fourth day of fasting. No investigation of the motor activity of the stomach of fasting persons seems to have been made previous to the report of the writer in 1914.

The following facts appear to question the validity of the view that fasting leads in a few days to paralysis of the hunger mechanism and consequent absence of hunger sensation.

1. It has been noted by physiologists and surgeons that the stomach of man and animal after a prolonged fast or on death from starvation is in a state of strong tonic contraction. Other factors being normal, a stomach in such state of contraction will give rise to hunger sensations.

2. The observations of the writer on two normal persons showed that the gastric hunger contractions and the hunger feeling persisted with practically normal intensity at least to the end of the fifth day of starvation.

3. The studies of Patterson, Rogers and the writer on fasting dogs and rabbits failed to confirm Boldireff's conclusions. The studies from our laboratory show that the gastric hunger contractions continue normal or even stronger than normal almost to the stage of death from starvation. Similar results were obtained by Patterson on fasting turtles and frogs.

4. If hunger and appetite disappear after a few days' fasting in animals below man, it is difficult to understand what induces the fasting animal to resume eating or to search and fight for food. A fasting person may resume eating from a sense of propriety or duty, but can we assume similar motives to action in the starving wolf or the starving caterpillar? Or is it likely that failure of the hunger mechanism after a few days' fasting obtains in man alone, in view of the complete parallel of other features of inanition in man and the lower animals? Wodsedalek has recently reported that a beetle (Trogoderma tarsale) will resume feeding after four to five years of enforced starvation during which period he may lose seven-eighths of his body substance.

Most of the evidence tending to show suppression of hunger after a few days' fasting consists of the statements of professional fasters or persons fasting to improve their health. Many of these persons have a fixed faith in fasting as a cure-all, hence they tend to ignore or deny most discomforts of starvation. The professional faster may do so in the spirit of bravado, and where the elements of faith or bravado are not in evidence the statement of the fasting person is obscured by the usual confusion of the sensations of the *pangs of hunger* with the *appetite for food*. In prolonged fasting the latter is interfered with in many persons by a persistent bad taste in the mouth.

We must recognize the possibility that the hunger mechanism may be depressed or altered in an individual by emotions and auto-suggestions. Observations on fasting animals are therefore not conclusive as the subject must be able to report his sensations synchronously with the presence or absence of the gastric hunger contractions.

A most striking case of prolonged suppression of hunger by emotional states in mammals has recently been recorded by Osgood, Preble and Parker. It would seem that the Alaskan fur-seal bull neither eats nor drinks during the entire breeding season (May to August).

> Many of them (the bulls) have been on the beaches from May and during the period from their arrival to the end of July or the early part of August, they touch no food. This fast of well over two months coupled with their incessant activity (fighting, sex activity) drains them of all their stored energy. They are reduced to skin and bones (p. 393).

From the time the bulls take their places on the beaches till they leave about early August, it is impossible to drive them away and they are never seen in this period in the water so that I think it perfectly safe to say that most bulls get no food for two months (June and July). If some come in April, as is stated by the islanders, the period may be as long as four months. The weather is cool or misty or rainy so that loss of water is not favored and abstinence from water is not so remarkable as that from food.[1]

The seal and the whale obviously obtain the water requirements for the body from the food itself (fish). In the absence of activity of the sweat glands the loss of water (from the lungs) in the seal is probably not much greater on land than in the sea. Does the tissue catabolism of the fasting seal yield a sufficient amount of water for the work of the kidneys for two to four months? Assuredly, a mature fur-seal bull confined in a suitable metabolism cage for two to four months during the breeding season would furnish very interesting data.

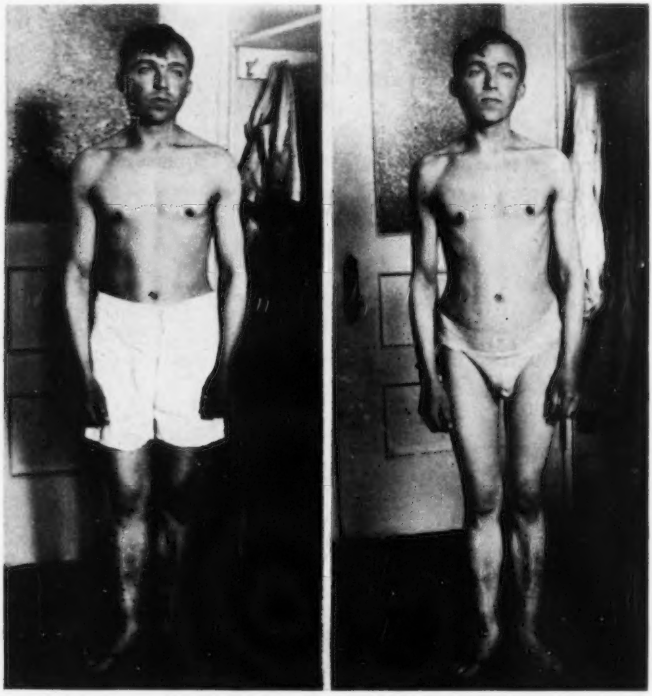
According to Boldireff, the stomach of the fasting dog exhibits occasional periods of secretion of gastric juice during the first three days of fasting, and after the third or fourth fasting day the gastric glands secrete continuously. Boldireff is inclined to ascribe the motor quiescence of the stomach of his fasting dogs to a reflex inhibition from the acid of this continuous secretion. The observations of Beaumont on Alexis St. Martin and those of Pavlov on dogs are largely responsible for the generally accepted view that in normal individuals the gastric glands are quiescent when there is no food or secretagogues in the stomach, and the appetite mechanism eliminated. We have shown that this view is erroneous for adult man and dogs. Hess and Taylor have shown that there is a continuous secretion of gastric juice in the newborn infant before the first feeding, and in young infants in the absence of food in the stomach. A continuous secretion of gastric juice by the normal empty stomach is therefore established. Is this continuous secretion augmented in prolonged fasting, as indicated by Boldireff's work on dogs? So far as we know this phase of inanition has never been investigated in man. This question is of importance not only in relation to the nature of inanition and to gastric physiology but as bearing on the possible rôle of the alimentary tract enzymes in starvation metabolism.

Mr. Frederic Hoelzel, the subject of this fasting study, is a man twenty-eight years old, graduate of a first class technical high school, and well

[1] Prof. G. H. Parker, personal communication. Prof. W. H. Osgood informs me that the bull may occasionally enter the water to reclaim an escaping cow, but he does not go far from land and does not feed.

versed both in the scientific and the popular literature on fasting, dietetics and nutrition.

During his last year in the high school (age 18), he suffered a breakdown in health, with insomnia, digestive disorders, great mental depression and a loss of 30 pounds in weight in the course of a year. The



A B

Fig. 1. Photograph of Mr. F. Hoetzel. *A*, before; *B*, at the end of the fifteen days' fast.

specific cause of this breakdown was not determined. The digestive disorders directed his attention along dietetic lines. He states that he has never completely recovered the mental and physical wellbeing enjoyed before this breakdown. He believes that starchy foods particularly disagree with him (causing flatulence). He has tried from time to

time to improve his health by starvation, fasting many times for periods of three to four days, at one time for a period of eight days, and once, three years ago, for a period of twenty-six days.

With the view of obtaining cure for these real or fancied digestive disorders as well as to render fasting more easily carried out, he has tried such food substitutes as "loam, sand, glass beads, silk, agar-agar, whole grain and seeds, bran, raffia, artificial cellulose and cotton fiber or kapoc."[2] He found the most satisfactory food substitute to be cotton fiber, cut into short lengths and flavored with salt, vinegar, citric acid, fruit juices or other food extractives. For the last year his diet has consisted mainly of fruits, vegetables and nuts, with some cream and eggs, and cotton fiber to make up bulk or "staying" quality.

Before starting this fast Mr. H. was given a thorough physical examination, including x-ray of the stomach by Dr. A. B. Luckhardt and Dr. F. C. Becht. The only defects discovered were some enlargement of the lymph glands of the neck, a tooth abscess and an unusual thickening and roughness of the skin, particularly of the lower extremities. He appeared somewhat nervous and diffident in the presence of strangers but looked the part of a well-nourished man, despite his own statement that he felt below par physically and mentally. He also felt convinced that his health would greatly improve after a prolonged fast. He thus undertook the fasting in the interest of his health and not primarily for the physiological observations made during the fast, although he appreciated the importance of the latter and coöperated in them with splendid intelligence and ability and with scrupulous honesty.

During the entire observation period—June 11 to September 1—Mr. H. lived in the laboratory.

Before starting the fast daily observations were made of the gastric hunger contractions and the gastric secretion for one week while Mr. H. continued on his regular diet. He states that for the past year he has practically taken only one meal a day, that is, from 6 to 11 p. m. The food taken June 11 to 17 was consumed in the same manner from 6 to 11 in the evening each day. There was always some food in the stomach at 8 o'clock the following morning. The stomach was usually empty of food (including the cotton) at 11 to 1 o'clock.

[2] Kapoc is the trade name for a very soft or silky cotton from the orient, used mainly for mattress filling.

Diet during control period, June 11 to 17

DATE AND MATERIAL	QUANTITY	CALORIES
June 11.		
Cream	1 pint	822
Eggs	132 grams	220
Nuts	77 grams	650
Flavor (maple sugar and cocoa with water)	276 grams	552
Oranges	311 grams	155
Tomatoes	841 grams	200
Strawberries	1020 grams	387
Cotton fiber (Kapoc)	21 grams (dry)	0
		2986
June 12.		
Eggs	141 grams	231
Cream	1 pint	822
Nuts	26 grams	181
Oranges	147 grams	73
Tomatoes	877 grams	212
Strawberries	242 grams	359
Flavor (maple sugar and cocoa)	231 grams	463
Cotton fiber (Kapoc)	21 grams (dry)	0
		2341
June 13.		
Eggs	177 grams	289
Cream	1 pint	822
Nuts	40 grams	288
Oranges	200 grams	100
Pineapple	440 grams	200
Tomatoes	845 grams	200
Flavor	212 grams	624
Cotton fiber (Kapoc)	27 grams (dry)	0
		2523
June 14.		
Eggs	256 grams	245
Cream	1 pint	822
Nuts	26 grams	181
Oranges	140 grams	70
Peaches	165 grams	69
Cherries	136 grams	96
Strawberries	432 grams	165
Tomatoes	905 grams	217
Flavor		560
Cotton fiber (Kapoc)	24 grams (dry)	0
		2425

Diet during control period, June 11 to 17—Continued

DATE AND MATERIAL	QUANTITY	CALORIES
June 15.		
Eggs	100 grams	165
Cream	1 pint	822
Strawberries	732 grams	279
Blackberries	484 grams	280
Tomatoes	715 grams	172
Oranges	166 grams	75
Nuts	28 grams	185
Flavor		584
Cotton fiber (Kapoc)	18 grams (dry)	0
		2562
June 16.		
Cream	1 pint	822
Eggs	95.5 grams	160
Raspberries	481 grams	255
Strawberries	800 grams	304
Blackberries	132 grams	79
Tomatoes	706 grams	168
Nuts	70 grams	505
Flavor		423
Cotton fiber (Kapoc)	10 grams (dry)	0
		2716
June 17.		
Pineapples	704 grams	316
Oranges	335 grams	267
Cherries	278 grams	227
Strawberries	457 grams	172
Bananas	224 grams	224
Cantaloupe	716 grams	340
Tomatoes	706 grams	176
Peaches	176 grams	72
Raspberries	226 grams	119
Apricots	127 grams	106
Flavor		182
Maple sugar	38 grams	155
		2356

This was the last meal before the first fasting period. The quality and the quantity of the food (and cotton) consumed each day were determined by his appetite and hunger. The heat value of the foods was

not figured until a later date. But it will be seen that even on such an unusual diet and only one meal per day the average heat value of the food consumed each day for this preliminary period was 2,544 calories.

The motility of the empty stomach was recorded by means of a small balloon in the stomach connected with a chloroform manometer. The contents of the empty stomach and the continuous secretion of the stomach were collected by a modified Rehfus tube. Mr. H. had no difficulty in swallowing these instruments and retaining them in the stomach without discomfort for several hours (four to ten) at a time.

The neuro-muscular strength and endurance tests were made on a Story type of ergograph, the abductor muscle working against a weight of 700 grams.

Mr. H.'s daily routine during the two fasting periods was, in general as follows: Sleep or rest in bed until 9 to 10 a. m. Taking of stomach content and continuous secretion. Recording of the hunger contractions (several hours). Ergograph record. A detailed diary especially of his sensations and emotions written by Mr. H. himself. A short walk in the nearby park or a ride in an automobile. Reading in the evening from 8 to 10. He sometimes attended a nearby motion picture theatre evenings. Towards the end of his fifteen days' fast he became less inclined to leave his room, spending most of the time resting on the couch when not engaged in the physiological tests.

I. THE GASTRIC HUNGER CONTRACTIONS DURING THE PRELIMINARY CONTROL PERIOD. BULIMIA

The record showing the end of a typical period of gastric hunger contractions of Mr. H. during the preliminary or control week is reproduced in figure 2. There is nothing abnormal in these records for a man of his age and physical condition, except that the periods were, on the whole, unusually long (one to two hours). The periods frequently ended in incomplete gastric tetanus lasting from ten to fifteen minutes. Shorter periods of incomplete tetanus or strong tonus waves also frequently appeared before the end of the period.

It was quite evident, however, that Mr. H. felt these contractions as more painful and uncomfortable than the average normal person. Before coming to our laboratory he had ascribed these pains to the pressure of gases chiefly in the large intestine. He did not consider them hunger pangs although he knew that he could abolish them by taking food or filling the stomach with indigestible material.

Fig. 2. Record showing the end of a period of gastric hunger contractions of Mr. F. H., June 13, 1917, twenty hours after a large meal (see p. 127). These apparently normal contractions induced severe abdominal discomfort or pain and a mental condition probably identical with bulimia. Chloroform manometer, time = 50 minutes.

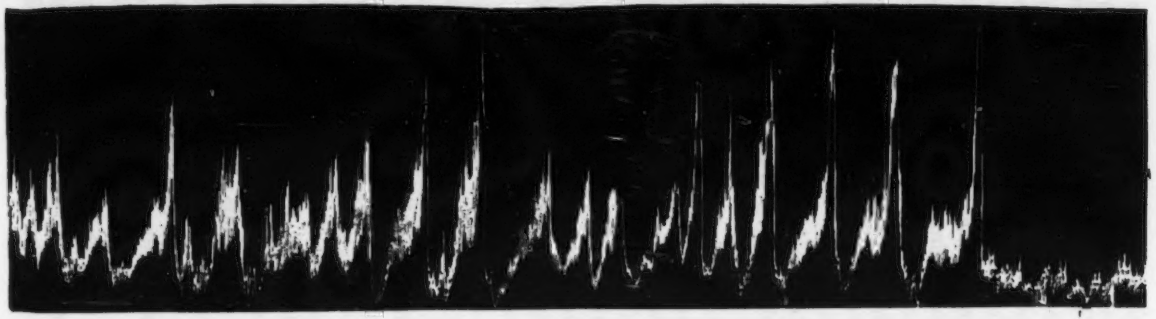


Fig. 3. Mr. F. H., June 20. End of a period of gastric hunger contractions on third day of fasting.

On June 13, when the record in figure 2 was taken, Mr. H. wrote in his diary: "These pains have frequently compelled me to end a fast, or deterred me from starting a fast. I don't see how any one could consider such pains as normal. When these contraction pains are most intense they appear to involve the entire abdomen and cannot be localized in the stomach." Mr. H. occasionally felt the pain, but less severely, even after beginning the ingestion of food.

It is quite clear that essentially normal gastric hunger contractions induced hunger pangs of abnormal painfulness in Mr. H. The reason for this condition is at present a matter of conjecture. There was no evidence of gastric or duodenal ulcers or of tabes. Hence the excessively painful character of the hunger contractions must have been due either to a more or less chronic hyperexcitability of the sensory nerves of the alimentary canal, or to a type of neurosis that led Mr. H. to give undue prominence to the visceral sensations in his conscious processes.

Mr. H. seems also to be deficient in the sensation of satiety.[3] The quantity of food in the form of bulky fruits and vegetables, in addition to bulky cotton, ingested by Mr. H. in order to feel "satisfied" would in the normal individual of the same size produce discomfort from overdistention of the stomach. Hence, unless Mr. H. takes indigestible material, like cotton fiber, together with his food, he necessarily overeats if he is to fill the stomach to the stage of satiety.

These facts lead me to think that Mr. H. presents a case of true bulimia. I have never seen a case of true bulimia, so diagnosed by a competent clinician, nor do I know of a case of true bulimia whose gastric motility has been studied by the balloon method. But these results on Mr. H. seem to show that bulimia does not necessarily involve an increase in the strength and duration of the gastric hunger contractions.

II. THE GASTRIC HUNGER CONTRACTIONS DURING FASTING

Our results may be given by the following analysis of the daily observations, together with the typical tracings reproduced in figures 3 to 9.

[3] Mr. H. states that food like bread or potatoes fails to satisfy him even when taken in very large quantities. The end of a meal is determined by the discomforts of an overdistended stomach, without any feeling of real satisfaction or satiety. The latter feeling usually does not come till the following morning.

First control period

June 11, 2–4 p.m. Two strong hunger periods (26 contractions) both ending in tetanus.

June 12, 12–4 p.m. Two strong hunger periods (37 contractions) both ending in tetanus.

June 13, 12–6 p.m. Three strong hunger periods (45 contractions) all ending in prolonged tetanus.

June 14, 12–6 p.m. Strong tonus and almost continuous hunger contractions (80) with short periods of tetanus.

June 15, 2–4 p.m. Two hunger periods (45 contractions).

June 16, 2–4 p.m. One prolonged hunger period (18 contractions) ending in tetanus lasting 10 minutes.

First fasting period

(Last meal 10 p.m., June 17)

June 18, 12–4 p.m. Three hunger periods (50 contractions), one ending in tetanus.

June 19, 5–8 p.m. Two mild hunger periods (37 contractions).

June 20, 5 hours. Four hunger periods (88 strong contractions).

June 21, 6 hours. Three hunger periods (53 strong contractions), one period ending in tetanus.

June 22, 6½ hours. Four hunger periods (40 fairly strong contractions).

June 23, 1½ hours. One strong hunger period (12 strong contractions).

June 23, 9 p.m. to June 24, 5 a.m. Five fairly strong hunger periods (50 contractions). No tetanus. Mr. H. slept during part of this observation period, becoming restless in his sleep and tossing about at the height of the strongest hunger contractions.

June 24, 3½ hours. Two moderately strong hunger periods (20 contractions).

June 25, 5 hours. Three strong hunger periods (38 contractions).

June 26, 5 hours. Three very strong and prolonged hunger periods (40 contractions).

June 27, 5 hours. Four moderately strong hunger periods (47 contractions), one period ending in moderate tetanus.

June 28, 8 hours. Three fairly strong hunger periods (35 contractions).

June 29, 4 hours. Three fairly strong hunger periods (25 contractions).

June 30, 4 hours. Three fairly strong hunger periods (35 contractions).

July 1, 5 hours. Three fairly strong hunger periods (30 contractions), one period ending in tetanus.

July 2, 5½ hours. Four fairly strong hunger periods (37 contractions).

July 3, 4 hours. One fairly strong and two feeble hunger periods (30 contractions), no tetanus, but marked and prolonged tonus variations, some of the tonus contraction periods lasting 10 minutes.

Second control period (July 4 to August 10)

During this period records of the motility of the empty stomach were taken for two to four hours each day. The tracings are practically identical with

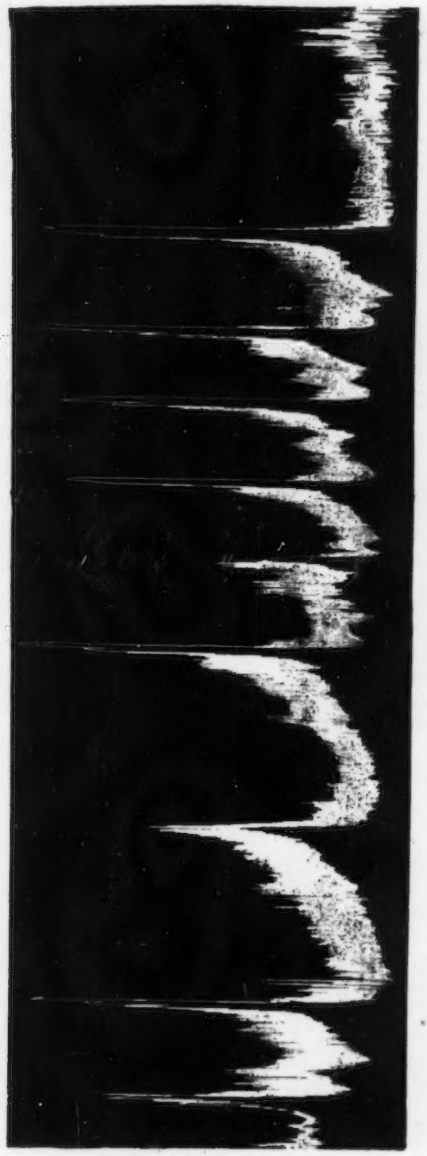


Fig. 4. Mr. F. H., June 23. End of a period of gastric hunger contractions on sixth day of fasting.

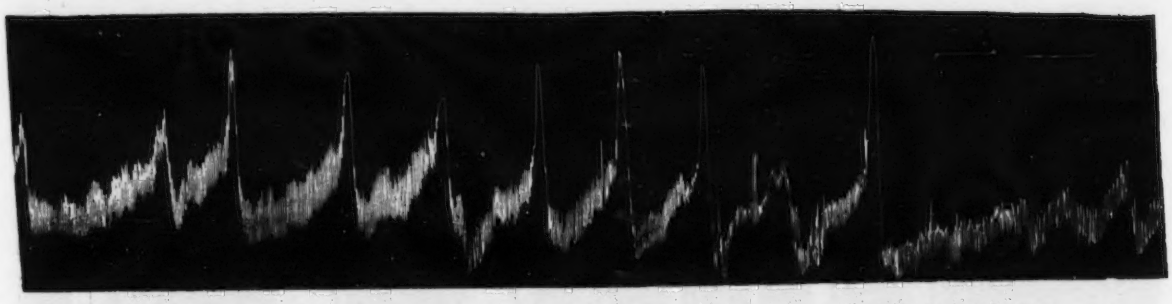


Fig. 5. Mr. F. H., June 26. End of a period of gastric hunger contractions on ninth day of fasting.

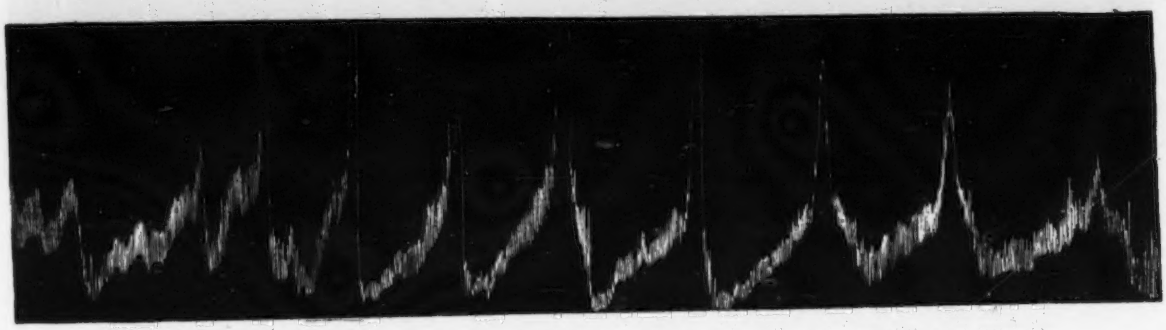


Fig. 6. Mr. F. H., June 29. End of a period of gastric hunger contractions on twelfth day of fasting.

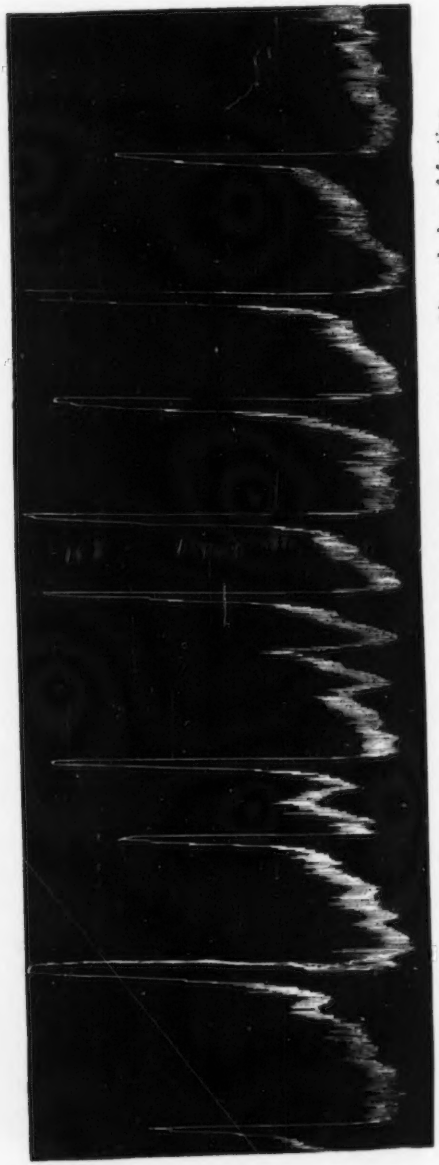


Fig. 7. Mr. F. H., July 2. End of a period of gastric hunger contractions on fifteenth day of fasting.

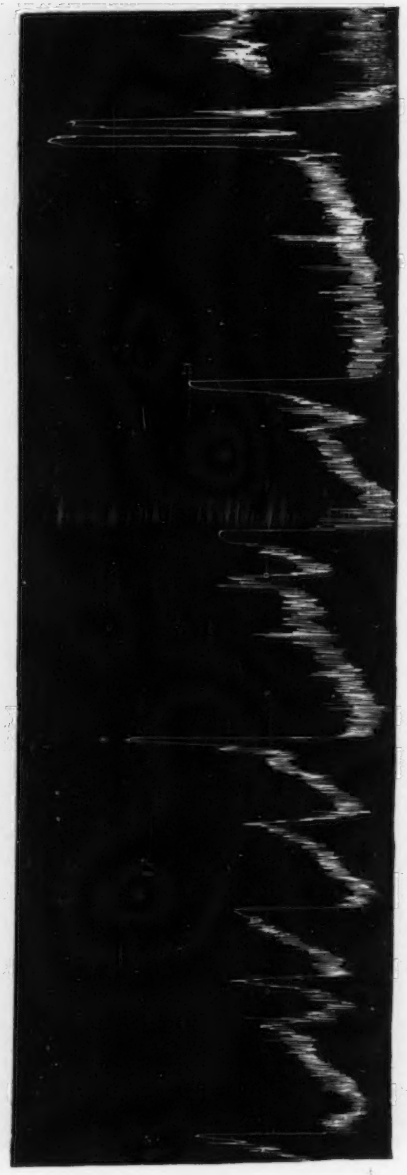


Fig. 8. Mr. F. H., July 3. End of a period of gastric hunger contractions on sixteenth day of fasting.

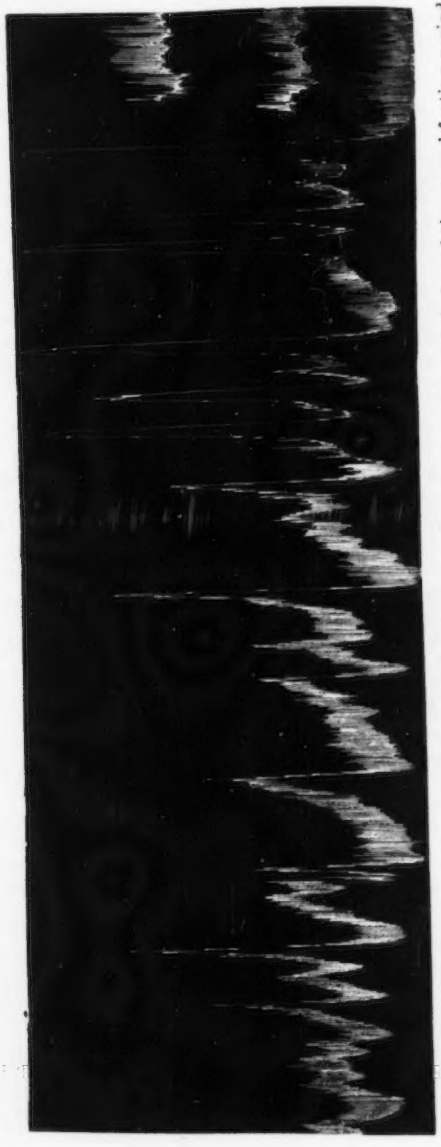


Fig. 9. Mr. F. H., August 18. End of a period of gastric hunger contractions on the eighth day of the second fasting period.

those of the first control period, so it is not necessary to give the data in detail. Periods of strong tonus and incomplete tetanus were again of frequent occurrence.

Second fasting period with daily ingestion of cotton moistened with gastric juice (August 11 to 18)

August 11, 10–12 a.m. One moderate hunger period (11 contractions).
August 12, 12–5 p.m. Four strong hunger periods (36 contractions).
August 13, 12–7 p.m. Six strong hunger periods (58 contractions).
August 14, 10.30 a.m.–2 p.m. Three strong hunger periods (33 contractions).
August 15, 11–12 a.m. One strong hunger period (15 contractions).
August 16, 11.30 a.m.–5 p.m. Four strong hunger periods (60 contractions).
August 17, 12.30–3.30 p.m. Practically continuous hunger period (40 contractions and 3 incomplete tetany periods, one lasting 20 minutes).
August 18, 7–11 a.m. Practically continuous hunger periods (45 contractions and 2 incomplete tetany periods).

Third control period (August 19 to September 1)

The daily record of the gastric hunger contractions during this period are practically identical with those of the previous control periods. Detailed analysis is therefore superfluous.

At the rate that Mr. H. was losing weight during the first fast (nearly 500 gr. per day) his second fast, reducing his body weight to 47.5 kgm., is equivalent to adding six to eight fasting days to his first fasting period, as his body weight at the end of that period was 50.57 kgm. Our results thus permit the conclusion that *the gastric hunger contractions persist with no appreciable decrease or increase in vigor, at least during the first twenty days of complete fasting in man.* This conclusion is further strengthened by the previous studies on fasting in man and dogs reported from our laboratory.

III. THE SUBJECTIVE FEELINGS OF HUNGER AND APPETITE DURING THE FAST

Mr. H. was conscious of the gastric hunger contractions throughout the fasting, and the periods of strong continued gastric tonus and incomplete tetanus were felt as a continuous uncomfortable tension. The more severe tetany periods made him very restless and uncomfortable and occasionally induced sweating. But on the whole *the gastric hunger contractions, although of normal duration and intensity, were less uncomfortable or painful than during the control periods when he consumed sufficient food to maintain or even increase the body weight.*

Mr. H. is also convinced that he felt the gastric hunger contractions throughout his twenty-six day's fast, carried out three years earlier. He is inclined to the belief that fasting men who report feeling no hunger

after the first three days' abstinence from food do not associate the sensation produced by the gastric hunger contractions with hunger, but regard it as pain or discomfort from gastro-intestinal disorders.

The state of the appetite for food during fasting appears to depend on the condition of the mouth. The mouth is frequently foul and the tongue coated, despite repeated washing of the mouth and brushing the teeth. The following notes from Mr. H.'s daily record are typical of his appetite condition:

Third fasting day. No salivation on seeing fruit. Rather indifferent to eating.

Fourth fasting day. No salivation on seeing food or seeing people eat.

Fifth fasting day. Seeing food induces some salivation. No strong desire for food.

Sixth fasting day. No strong desire for food.

Seventh fasting day. Some salivation on thinking of food during a period of hunger contractions.

Eighth fasting day. Fruit displays look very good to me, but the bad taste in the mouth seems to prevent appetite.

Eleventh fasting day. Would be glad to resume eating.

Thirteenth fasting day. Odor and sight of food very agreeable, but mouth conditions seem to repress appetite.

Fifteenth fasting day. Seems to crave bulk and flavor, but not necessarily nutrient foods.

First day of breaking the fast. Surprised that I do not crave food very much,—want flavor and bulk.

On the first day of breaking the fast he wrote: "Food (fruit) does not taste as good as I anticipated." Nevertheless he stated at the end of both fasting periods that "*the dominant element in consciousness throughout the fast is ideas or thoughts of food and eating.*"

IV. THE CONTINUOUS SECRETION OF GASTRIC JUICE DURING PROLONGED FASTING

Our data on this phase are summarized in tables 1 and 2. These data permit the following conclusions:

1. There is no increase in the quantity of the contents of the empty stomach in fasting but the gastric content is more frequently mixed with bile and shows, on the whole, a higher acidity.

2. There is no definite increase in the rate of the continuous gastric secretion in fasting but the secretion shows, on the whole, a higher acidity. This is evident during the fifteen days' fast, but there is no increase in the acidity during the second fast when Mr. H. ingested cotton fiber daily.

These results on man are corroborated by studies on fasting dogs recently completed in our laboratory by Dr. G. F. Sutherland. It must be admitted, of course, that individuals may show gastric hypersecretion during fasting owing to special conditions induced by the fast. But Boldireff is evidently in error in concluding that fasting invariably leads to continuous hypersecretion after the third or fourth day.

TABLE 1

Summary of observations on the contents of the empty stomach of Mr. F. H.

	NUMBER OF OBSERVATIONS	CONTAMINATION BILE	QUANTITY CUBIC CENTIMETERS			ACIDITY					
						Free			Total		
			Low	High	Average	Low	High	Average	Low	High	Average
		per cent	*cc.*	*cc.*	*cc.*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Period before fasting	6	16	10	50	26	0	0.09	0.05	0.03	0.18	0.12
First fasting period (15 days)	23	92	10	65	28	0.09	0.34	0.13	0.11	0.34	0.22
Period after fasting (27 days)	25	28	10	70	27	0	0.13	0.07	0.08	0.21	0.13
Second fasting period (8 days)	10	80	12	55	30	0	0.16	0.08	0.10	0.25	0.14
Period after second fasting (10 days)	10	30	10	45	31	0	0.16	0.08	0.06	0.22	0.14

TABLE 2

Summary of observations on the continuous secretion of gastric juice in prolonged fasting, Mr. F. H.

	NUMBER OF OBSERVATIONS	CONTAMINATION BILE	SECRETION RATE PER HOUR			ACIDITY					
						Free			Total		
			Low	High	Average	Low	High	Average	Low	High	Average
		per cent	*cc.*	*cc.*	*cc.*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Before fasting	4	50	25	75	50	trace	0.15	0.10	0.10	0.25	0.15
First fasting period (15 days)	21	85	28	126	64	0.08	0.32	0.19	0.12	0.39	0.27
After fasting (27 days)	25	12	40	224	140	0.04	0.15	0.08	0.08	0.20	0.14
Second fasting period (8 days)	10	50	40	120	72	trace	0.16	0.06	0.06	0.21	0.12
After second fasting period	10	20	40	168	92	trace	0.16	0.07	0.06	0.19	0.14

V. ADDITIONAL NOTES ON THE PHYSIOLOGY OF FASTING

The blood pressure, the strength and endurance tests and the total nitrogen elimination during the two fasts were recorded, not with the view of revealing anything new, as we have a number of well-controlled studies on fasting men in the literature, but for the purpose of *a*, checking up on any special peculiarity in Mr. H., and *b*, as a control of his actual fasting. It will be remembered that Mr. H. was not locked up when not under my observation.

A. The blood pressure

DATE	DIASTOLIC	SYSTOLIC	PERIOD
June 18	95	110	First fasting period
June 25	86	100	
June 26	88	92	
June 27	86	90	
June 28	86	94	
June 29	86	92	
June 30	72	88	
July 1	74	90	
July 3	76	94	
July 6	72	84	Period of very low protein diet (essentially fruits and vegetables)
July 9	80	94	
July 10	80	92	
July 13	86	100	
July 14	86	94	
July 15	80	98	
July 17	88	104	
July 20	76	88	
July 23	88	104	
July 30	88	102	
August 19	78	89	End of second fasting period
October 16	84	110	

The data show the same tendency to a lowering of the blood pressure during the fast as has been noted by previous investigators.

B. The ergograph records. (Figs. 10 to 13.) The thirty minutes daily ergograph records show some apparent increase in strength and a marked increase in endurance gradually developed during the fifteen days' fast. Cramplike pains in the abductor muscles while taking the

Figs. 10 to 13. Ergograph records (abductor indices muscle working against 700 grams) of Mr. F. H. Duration of test = 30 minutes.

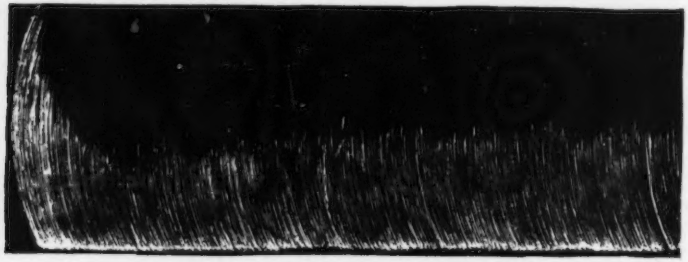


Fig. 10. June 17, day before starting first fast.

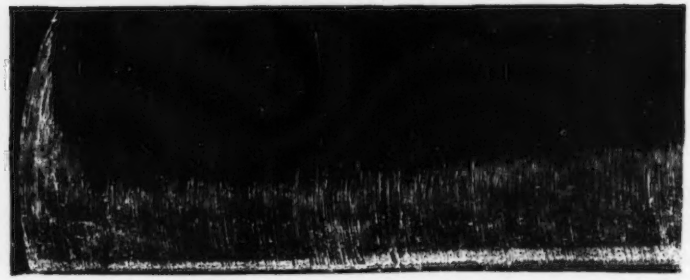


Fig. 11. June 22, fifth day of fasting.

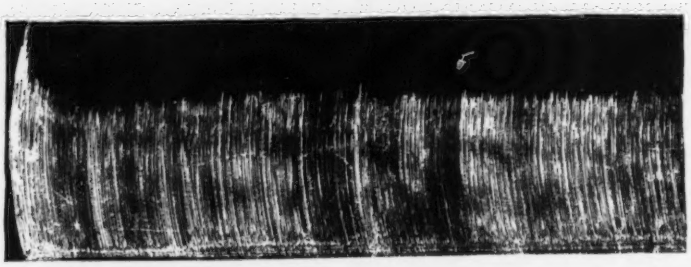


Fig. 12. June 28, eleventh day of fasting.

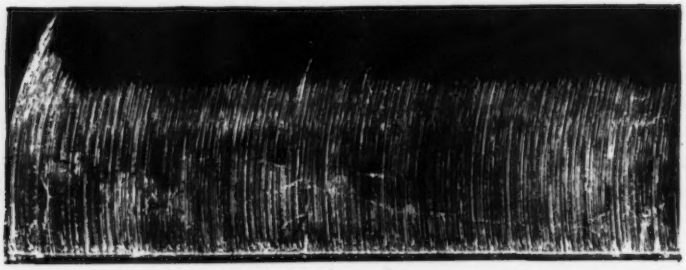


Fig. 13. July 3, fifteenth day of fasting.

records became less. This evident improvement in the ergograph records during the first fast were probably due in part to training of the particular neuro-muscular group involved and the mental factor or conviction on the part of Mr. H. that starvation improves the physical condition of a person. Taking Mr. H.'s physical condition as a whole there is no question that the fast produced gradual weakness and disinclination to physical or mental effort, such as reading, walking or working.

C. The water intake (tables 3 and 4). The daily ingestion of water was governed not by the thirst sensation primarily, but by the desire to increase elimination and the hope to improve the condition of the digestive tract.

D. The nitrogen elimination (tables 3 and 4). During the interval between the two fasting periods (July 4 to August 10) Mr. H.'s diet consisted essentially of fruit juices and vegetables (mainly tomatoes), with an occasional pint of cream and cotton fiber. On this diet the daily excretion of nitrogen in the urine varied from 2.5 to 4.5 grams., representing a protein metabolism of 15 to 30 grams per day. On this diet he gained nearly 2 kilos in the thirty seven days.

Both fasting periods showed a marked drop in urine nitrogen on the second and third days. A similar drop in the urine nitrogen appeared in Levanzin's fast under Benedict. During the fifteen days' fast the average daily output of urine nitrogen was 7.18 grams or 0.132 grams per kilo body weight, representing a daily average protein metabolism of about 45 grams. During the second fast of eight days the nitrogen output was considerably lower, or 5.70 grams per day (0.116 grams per kilo body weight), representing a daily metabolism of 35.62 grams of protein.

The striking feature in the present case is the low protein metabolism in the fasts. Benedict's subject, Mr. Levanzin, with a body weight practically identical with that of Mr. Hoelzel, excreted more than 8 grams of nitrogen in the urine up till the end of the thirty days' fast, and during the first fifteen days of the fast the nitrogen output averaged about 10 grams per day.

E. Movement of the bowels. During the fasting period June 18 to July 3 movements of the bowels occurred on the following days:

June 18. Ordinary feces.
June 19. Ordinary feces.
June 23. Mucus and food debris (strawberry seeds, etc.). About 3 cc.
June 26. Mucus and food debris (vegetable fibers, seeds, etc.). About 8 cc.
June 27. Mucus and a few traces of food debris. About 10 cc.

June 28. Mucus and a few traces of food debris. About 15 cc.
June 29. Mucus and a few traces of food debris. About 10 cc.
June 30. Mucus and a few strawberry seeds. About 2 cc.
July 1. Mucus and a few strawberry seeds. About 15 cc.
July 2. Mucus and a few strawberry seeds. About 25 cc.
July 3. Mucus, no trace of food debris. About 60 cc.

Mr. H. made special effort to force a bowel movement each day. No enemas were used. After June 19 the material passed was mostly soft bile-stained (brown) mucus with a few vegetable fibers and fruit seeds from his food taken before fasting. The material was semi-liquid, but there was no diarrhoea at any time. Gas was passed per rectum every day, and the solids passed had fecal odor (on some days very offensive) even on the fifteenth day of starvation.

The striking fact is the retention of traces of food débris (strawberry seeds) in the alimentary tract for at least fifteen days.

After June 19 Mr. H. had at no time the normal desire to defecate. All the bowel movements were forced, several attempts usually succeeding in one passage each day except as noted above.[5] The quantity of fecal material passed each day was very small, and without the special effort Mr. H. might have gone through the entire fast without a passage, as has been recorded in the case of other fasting experiments.

During his second fasting period, August 11 to 18, when he ingested a certain quantity of cotton moistened with gastric juice, there were bowel movements as follows:

August 11, 6.20 a.m., 1.00 p.m., 11.10 p.m.
August 12, 6.45 a.m., 12 noon.
August 13, 7.30 p.m. (Food debris and cotton.)
August 14, 11.15 p.m. (Cotton with a few grape seeds.)
August 15, 11.15 p.m. (Cotton; no food debris.)
August 16. Attempts at bowel movement without results.
August 17, 11.30 a.m. (Cotton; no food debris; slight fecal odor.)
August 18, 11.30 a.m. (Cotton; no food debris; slight fecal odor.)

The ingestion of cotton evidently sweeps out completely the food débris in the alimentary tract in three to five days. It may also reduce the quantity of intestinal bacteria by mechanical action. The form in which cotton taken by mouth is passed per rectum may be gathered by the fact that the smallest bolus passed measured 0.5 cm., the largest 3.5 cm. in diameter.

[5] Mr. H. states that during his twenty-six days fast three years ago he usually succeeded in forcing one bowel movement per day.

TABLE 3

The water intake and output of urine and urinary nitrogen of Mr. F. H. during the first fasting period, June 18 to July 3

DATE	ROOM TEMPERATURE	BODY WEIGHT	URINE			WATER INTAKE
			Quantity	Specific gravity	Total nitrogen	
1917			*cc.*		*grams*	*cc.*
June 18		57.72	1200	1016	11.03	700
June 19		56.37	630	1020	3.97	900
June 20	64–70	55.56	800	1023	8.02	1350
June 21	70–72	54.86	1110	1015	10.07	1400
June 22	64–66	54.56	1060	1020	10.53	1100
June 23	69–73	53.89	580	1030	8.85	1300
June 24	64–66	53.59	1020	1020	9.31	1000
June 25	68–74	53.10	760	1022	8.23	1700
June 26	76–78	52.62	910	1017	7.97	1400
June 27	74–76	52.14	1300	1014	7.27	1800
June 28	74–76	51.82	1250	1012	6.81	1500
June 29	68–70	51.52	1225	1015	6.99	1300
June 30	68–74	51.11	1100	1016	6.50	1300
July 1	68–70	51.08	1210	1012	6.22	1800
July 2	64–68	50.89	1000	1012	6.34	1100
July 3	68–70	50.57	1090	1013	6.85	700
July 4	68–20		550	1020	4.73	

TABLE 4

The water intake and the output of urine and urinary nitrogen during the second fasting period, August 11 to 18

DATE	ROOM TEMPERATURE	BODY WEIGHT	INGESTION OF COTTON	INGESTION OF WATER	URINE		
					Quantity	Specific gravity	Total nitrogen
1917			*grams*	*cc.*	*cc.*		*grams*
August 10					2600	1009	3.70
August 11	66–70	52.12	15	200	2200*	1011	2.52
August 12	70–72	51.09	19	400	560	1018	1.78
August 13	73–74	50.38	35	700	225	1030	3.18
August 14	72–74	49.80	55	500	400	1022	5.87
August 15	70–72	49.07	35	500	380	1025	6.70
August 16	74–78	48.38	48	700	310	1028	5.81
August 17	72–74	48.16	42	700	370	1027	6.39
August 18	74–80	47.83	50	900	410	1026	6.70
August 19	78–80	47.50			650	1018	6.69
August 20					500	1016	2.29

* On August 10, the day before starting the second fast, he consumed the following quantity of food: ½ pint cream; 5 ounces maple sugar; 10 bananas; 1 apple; 9 oranges; 1 pound cherries; 1¾ pound grapes; 2 cantaloupes; 3 lemons; 1 tomato; 1 quart red raspberries; 2 ice cream "sundaes;" 25 cc. water.

F. The mouth condition. In the first fasting period Mr. H. noted a disagreeable or foul taste in the mouth, coated tongue and tenderness of the gums (spontaneous bleeding or bleeding on rubbing the gums with the tongue). These conditions persisted throughout the fasting period and undoubtedly modified or suppressed his appetite for food as appetite involves the memory of pleasant gustatory and olfactory sensations.

Similar mouth conditions developed during the second fast, August 11 to 18. They are not due to lack of salivation or to neglect of common mouth hygiene.

G. General mental condition. The prevailing feeling during both fasting periods was one of gradually increasing weakness. The degree of depression varied from day to day, but the expressions, "feel all in" or "all fagged out" recur again and again in his diary. This depression was evident both in his mental and physical behavior. A certain degree of mental disturbance by the fasts is also indicated by the fact that Mr. H. became readily provoked and discouraged. But despite the feeling of weakness the mind was frequently unusually clear.

His sleep was frequently disturbed by the hunger pangs, by headache and by vasomotor irregularities ("hot flashes"). He was not able to sleep at all when the hunger contractions were severe.

Mr. H. was convinced that his sense of smell became more acute during the fasts. The *odor* of foods was the most potent stimulus to appetite. Sex interest and sex emotions were depressed.

SUMMARY AND CONCLUSIONS

1. During the fifteen days' complete fast and the subsequent eight days of abstinence from food with daily ingestion of cotton fiber, the gastric hunger contractions of Mr. Hoelzel continued with practically normal rhythm and intensity, but the subjective sensations induced by the gastric contractions appeared to be somewhat weakened and tinged with an element of general epigastric distress or sick stomach. The view that the hunger mechanism fails early in prolonged fasting is therefore not tenable as a general law.

2. The appetite sense or desire for food was modified or obscured by a tendency to a persistent bad taste in the mouth that developed during the fast. But Mr. Hoelzel states that the dominant element in consciousness during the fast was nevertheless thought of food and eating.

3. The contents of the empty stomach and the continuous gastric

juice secretion during the fasts show a tendency to a slight increase in acidity and greater frequency of regurgitation of duodenal contents into the stomach, but there is no significant increase in secretion rate over that of the control periods. In other words, the normal process of continuous gastric secretion of the empty stomach in not noticeably augmented in prolonged starvation.

BIBLIOGRAPHY

(1) Cannon and Washburne: This Journal, 1912, xxix, 441.
(2) Carlson: This Journal, 1912, xxxi, 151, 175; 1914, xxxiii, 95; 1915, xxxvi, 50; The control of hunger in health and disease, Chicago, 1916; Interstate Med. Journ., 1917, xxv, no. 5.
(3) Benedict: A study of prolonged fasting. Carnegie Inst. of Washington, 1915.
(4) Boldireff: Arch. d. Sci. Biol., 1905, xi, 1; Ergebn. d. Physiol., 1911, xi, 186.
(5) Hess: Amer. Journ. Dis. Children, 1913, vi, 264.
(6) Luciani: Das Hungern, Leipzig, 1890.
(7) Osgood, Preble and Parker: Bull., U. S. Bureau of Fisheries, 1915 xxxiv, 19.
(8) Parker: Sci. Monthly, 1917, 385.
(9) Patterson: This Journal, 1915, xxxvii, 316.
(10) Rogers: This Journal, 1915, xxxvi, 183.
(11) Storey: This Journal, 1903, viii, 355.
(12) Taylor: Amer. Journ. Dis. Children, 1917, xiv, 258.
(13) Wodsedalek: Sci., 1917, xlvi, 366.

ADDENDUM

Chicago, September 1, 1917.*

Dr. A. J. Carlson,
Chicago, Ill.

Dear Sir:

As I may not find it convenient to resume some of the past experimentation at a later date I am taking this occasion to give a summary of the feelings or ideas which have prompted me to take the somewhat irregular course regarding feeding and fasting in the past few months.

The first week (the control) fairly represents my feeding habits during the previous three months—with the exception that on Sundays and holidays I always began eating within an hour or two after rising. In order to hold to the regime represented I would ordinarily need to be occupied with work involving

---

* At the end of six weeks of hard physical labor (harvesting). On this date Mr. H's body weight was 61.84 kgm.

partly physical activity so as to distract my attention from the practically constant mild headaches and abdominal pains (gastric and other).

My first fast (fifteen days) was taken and carried to the end of the fifteenth day mainly because I felt that I had pledged myself to go without food that long. If no one but myself had knowledge of this resolve I believe that the general weakening and depression would have led me to stop before the sixth day. I never carried a pure fast longer than four days when no one else knew my intentions.

Although I entertained the secret hope of fasting continuously for thirty days or more, I began eating on the sixteenth day to get rid of the depression and weakness. I also discontinued this fast because I expected to find fasting more agreeable later while using cotton fiber. As the fast progressed there developed a growing conviction or feeling that food would be agreeable, but this indication of hunger seemed to be overshadowed by the general depression, weakness and foul mouth condition.

The eight-day-fast (using cotton fiber) with and without my own gastric juice) is the longest fast I have taken where I felt that I was free to stop as soon as it became disagreeable. If I had not been underweight with the disagreeable experiences of the first fast fresh in mind, I might have continued this fast much longer.

My subsequent attempts to use only lemon juice, etc., with fiber could not be carried out because it seemed that the small amount of nutriment used coaxed the appetite or hunger and made it harder to abstain from more substantial food.

As already indicated in earlier discussions with you I believe that the so-called hunger pangs or intense gastric contractions are not an indication of hunger but reflect a more or less abnormal gastro-intestinal condition. It seems to me that hunger has mainly a psychic or mental indication originating from the chemical blood and tissue state. However this mental hunger may be intensified by gastric contractions. The contractions impress me as a form of local pain when hunger (mental) is vague or absent.

A muscular or tissue sense of hunger may be indicated by the feeling of emptiness which is particularly prominent the first few days of fasting. But as this feeling disappears as the fast progresses (probably by readjustment of muscle and tissue tone over the abdomen) I believe this is abnormal (habit hunger?). However hunger appears to be a complex phenomenon which can probably be separated into hunger for proteins, for carbohydrates, etc., as it does not seem as though satiety can be produced until all the elements of hunger indicated at any time are satisfied by the amount and kind of food craved.

The foregoing opinion of what hunger is does not prevent me from making attempts to allay the gastric pangs. The most simple and direct method is to stop these intense contractions by eating food, whether hungry or not. But as eating without hunger makes gastro-intestinal conditions worse it has seemed wiser to allay the pangs by taking some food substitute, as cotton fiber, etc. And as I believe that the gastric contractions would go on without affecting consciousness under ideal physiological gastro-intestinal conditions, I attempt to regain this state by fasting, adjustment of diet, etc.

Respectfully yours,

FREDERICK HOELZEL.

AEQUIRADIO-ACTIVITY

H. ZWAARDEMAKER

From the Physiological Department, The University, Utrecht, Netherlands

Received for publication October 3, 1917

It is remarkable that the animal tissues are made up of a comparatively small number of elements. All in all there are twelve (of the first *Mendejeleff* group *H*, *Na* and *K*; of the second *Mg* and *Ca*; of the fourth *C*; of the fifth *N* and *P*; of the sixth *O* and *S*; of the seventh *Cl*, and of the eighth *Fe*). Two of them possess a very characteristic atomic property, which no doubt enables them to exert an influence of their own. They are iron, which is ferro-magnetic, and potassium, which is radio-active.

The ferro-magnetism of iron is often concealed in the compounds (also in those in which iron occurs in the human body, namely, hemoglobin) behind the diamagnetism of the other atoms, so that the whole complex becomes diamagnetic again. The radio-activity of potassium, however, remains in the compounds so that it may be expected to reveal itself in the organism anywhere and at any time.

True, the radio-activity in potassium is but little pronounced. According to the discoverer, N. R. Campbell, (1) it renders a photographic plate appreciably black only after fifty-six days. It emits exclusively β-rays of a high penetrating power, but their number is so small that the ionising power exerted by a layer of potassium-salt upon the air of the ionising chamber is a thousand times lower than that of a similar layer of uranium-oxid, insofar as the β-radiation is concerned. α-rays are not emitted by potassium at all, so that potassium-salt, unlike uranium-salt, in such an experiment need not be screened from the ionising chamber by tinfoil.

Upon the basis of these facts it is possible to establish by calculation the intensity of the radio-active radiation of this element to be found in all animal tissues, which determination is of great moment for physiology. The ionising-power of potassium is one thousand times weaker than that of uranium which, in its turn, is again about a million times weaker than radium. The more correct ratio is 4: 10^9 (thousand millions) (2). But the radium under

discussion contained the elements to which it is progressively converted. Its radio-activity, irrespective of the accessory products, is estimated at 1.38×10^6 erg per second and per gram. The β-rays come in for 3.2 per cent or 4.4×10^4 erg per second (3). This was the β-energy with which we had to do in the determination of the ionising-power through aluminium foil. To establish the ionising-power of potassium we must divide the energy-quantum of radium by 250,000,000, the result being 17.6×10^{-5} erg per second. This, however, applies only to the case when the β-rays of potassium are of the same penetrating power as those of radium. It is, however, eight times stronger and the energy of each ray about four times greater. Consequently the energy-value per gram of metal rises for potassium to 7×10^{-4} erg per second. Meanwhile we have still to correct an error, for in our calculation we presumed to have to do with pure radium (4) whereas we actually worked with radium and accessory products when the parallel was drawn. The energy of this radium is supposed to be fifty times that of pure radium (4). The energy of one gram of potassium lies, according to my calculation, in the neighborhood of 3.5×10^{-2} erg per second. Should it be supposed that the considerable penetrating power of the potassium-radiation is not sufficiently established, or that it ought not to be taken up in the calculation, the last value is reduced to 0.8×10^{-2} erg. In our case we took the round value of 3.10^{-2} erg.

Closely allied to the radio-activity of potassium is that of rubidium. A salt of this metal renders the photographic plate black in one hundred days (5). The ionising-power is one five-hundredths that of uranium-oxid for β-rays (6). The two light metals have in common that each of them gives off exclusively negative particles. According to Rutherford, this absolute lack of α-radiation precludes the hypothesis that heavy radio-active elements are at the bottom of the phenomenon. Nor does the exposure to the action of light modify in any way the radio-activity peculiar to potassium and rubidium.

The ionising-power of rubidium being one five-hundredth of that of uranium-oxid through tinfoil, the energy of 1 gram of rubidium would be as great as that of about 1 gram of potassium, if not the penetrating power were found to be ten times smaller (Campbell). In this connection I think the energy of 1 gram of rubidium is to be fixed upon $2 \times \frac{1}{5} \times 3.5 \times 10^{-2}$ erg per second or about 1.7×10^{-2} erg per second. So the number of the β-rays sent out by radium is larger indeed but their effect is slighter because the velocity of the mobile negatively-charged particle is less.

The heavy radio-active elements are not found in the animal body unless they have been purposely introduced. Also rubidium fails. As a radio-active element, therefore, potassium stands entirely by itself in the organism, so that the question arises whether any specific effect can be detected.

With the intention to collect the necessary data to settle this question, I enjoined my assistant, Mr. T. P. Feenstra, to ascertain whether in the artificial circulating fluids of S. Ringer and his followers potassium could be replaced by the other radio-active elements. A similar investigation, but not guided by radio-activity, had been previously made by Ringer (7) himself for the first group of *Mendejeleff* and he compared his results with those obtained with potassium in aequimolecular concentrations. Rubidium proved to be the only element that answered the purpose. Our new point of view now urged us to work not with aequimolecular but with aequiradio-active dosages. We therefore calculated as well as we could, in the way indicated above, the radio-activity of the potassium and the rubidium that occurs in Ringer's solutions and subsequently measured the doses of the other radio-active elements to be examined, so as to make their total radio-activity agree with that of the potassium doses. The α-, the β- and the γ-rays were taken together, as it seemed to me hardly judicious to make an *a priori* selection of one of them. Most helpful was Rutherford's excellent textbook containing direct indications about the total radio-activity of uranium, thorium and radium, so that there was no necessity to calculate them in our own clumsy way. This, indeed, evolved a seeming inconsistency in the calculated K- and Rb-values on the one hand and the physically determined U- and Th-values on the other. Moreover, experimentation had to decide. Starting from the values we had calculated, Mr. Feenstra patiently and tactfully tried to find the practicable doses. After some shilly-shallying, my coworkers hit upon the following metal-doses per litre of circulating fluid, that is applied to the Kroneckered frog's heart (winter frog) (8):

Metal doses in milligrams per liter

K	Rb	U [4]	Th	Ra
53	105	12	24	3.10^{-5}

In our estimation the following energy-quanta correspond to these metal doses (9):

Energy-quanta come in per litre and per second (in 10^{-4} erg.)

K	Rb	U	Th	Ra
16	73	96	72	41

It will be seen that the metal doses are not perfectly aequiradioactive. They are of the same order, though. It should not be forgotten, however, how they originated, viz., first theoretical conjecture, then experimental searching. The said metal doses were contained in the following amounts of salt:

Potassium in 100 mgm. KCl per litre	53 mgm.
Rubidium in 150 mgm. KCl per litre	105 mgm.
Uranium in 25 mgm. $UO_2 (NO_3)_2$ per litre[1]	12 mgm.
Thorium in 50 mgm. Th $(NO_3)_4$ per litre	24 mgm.
Radium in 5 micromgm. radium salt per litre	3 micromgm.

Besides the radio-active ingredients they were in S. Ringer's artificial circulation fluids.

Calcium chlorid[2]	200 mgm.
Sodium bicarbonate	200 mgm.
Sodium chlorid	7 grams
Water	1000 grams

These five artificial circulatory fluids can keep the isolated Kroneckered frog's heart (winter frog) beating for hours. It is decidedly necessary, however, to take one precaution: in passing from one fluid to another, *to pass through a solution quite free from potassium.*

We proceeded as follows: First the Kronecker inflow-cannula, "à double courant," was slipped into the sinus venosus. The ligation was then performed midway between sinus and atrioventricular boundary. It now seemed as if the heart had been tied up by Stannius ligatures and so we had to make sure of the heart beating forcibly and regularly for a quarter of an hour. It was accordingly suspended after Gaskell-Engelmann and registered graphically, if necessary. Then followed a circulation with common Ringer's mixture deprived of potassium-salt. The result was a more or less abrupt or a gradual standstill in diastole, on the average after a half hour. Great attention was given to the utmost purity of the various salts and above all due care was taken to use a real potassium-free Ringer's solution when procuring the standstill of the heart. This was far from easy as commercial sodium chlorid, even when obtained in a supposed pure condition of well-known factories, mostly contains potassium. In this procedure the colorimetrical method recommended by Howell and

[1] Inclusive of water of crystallization.

[2] Sometimes quite free from water, then again with 25 per cent water.

Duke (10) stood us in good stead. We deemed it sufficient if the potassium-free mixture contained less than 1 mgm. of potassium per litre.[3]

The precaution indicated above is indispensable for, if omitted, the forcibly beating heart will cease its pulsations directly when a K- or Rb-fluid is succeeded by one with the heavy metals or the reverse. The light and the heavy metals may, however, be *inter*changed without a potassium-free interval. This does not interfere with a continuance of the regular and forcible pulsation. The solutions may even be mixed in equal amounts. Contrariwise, if one administers a mixture in equal amounts of a Ringer's solution with light metal and a Ringer's solution with heavy metal, the heart will come to a complete standstill at once (11) if one should experiment with the fresh organ or after a short potassium-free circulation. This I have named "the first paradox" of the three that we have encountered in this study (12).

A heart accidentally brought to a standstill in one of these procedures resumes its action the moment when the interfering fluid has been replaced by one that has been deprived of potassium and uranium both. During the standstill the susceptibility to a mechanical stimulus is most often retained. A peculiarity regarding electrical stimuli has been described by us in detail in a previous paper (13).

As indicated at the beginning, we tried to find out whether in the artificial circulating fluid the potassium is to be substituted by the other radio-active elements. This we found to be the case. The remarkable aequi-activity manifesting itself in the appropriate doses gave rise to the presumption that the substitution is feasible only on the ground of the radio-active, atomic property of these elements and is not to be ascribed to any other factor. This also led us to try the addition of emanation to the potassium-free Ringer's mixture. A quantum of 100 Mache-units proved to yield a positive result. Moreover here also the first paradox was obtained, so that we could place emanation on the same level with the heavy radio-active metals that in previous experiments we had added to the artificial circulating fluids.

It seems to me that an important conclusion may be deduced from the experiments with radium-containing fluids and those with emanation. Apparently the influence that comes into play here is of a different nature from that dominating the famous experiments on

[3] In some experiments potassium was present to the amount of 2.5 mgm. per litre.

balancing ions of J. Loeb (14) and his coworkers, as is evident from the fact that the mass may, so to speak, be eliminated both in the case of radium-salt, which was added only to an amount of 5 micromgm. (5×10^{-9} gram) per litre, and in the case of emanation. If the balance is caused by the concourse of mass effects between the various ions, in regard to the proteins, when there are no masses the influence of chemical affinities and valences cannot clinch the matter. In this case there are no masses, consequently we have to seek the influence at play elsewhere. Nevertheless in others when the quanta are easily measurable, with uranium as well as with thorium, the balancing power remains. When the calcium in the circulating fluid was augmented, the uranium and the thorium doses had to be increased. Nay, even the mixture-ratios between potassium and uranium which, being mutually antagonistic caused a standstill instead of automaticity of the heart, were slightly modified under the influence of the calcium (15). Also balancing appeared when calcium was replaced by strontium. W. H. Jolles (16) established this by testing the electrocardiogram as well as the movements. With strontium in place of calcium, circulating fluids may be made from the radio-active elements, in which the entire frog's heart excised from the body, continues to beat yielding a normal electrocardiogram. We started similar experiments with summer frogs but did not complete them. Evidently the composition of the circulating fluid has to be modified. The calcium content has to be increased a little (to 250 mgm.) per litre exclusive of the water of crystallization) whereas the potassium content is to be largely diminished (from 100 mgm. of potassium chlorid to 30 or 50 mgm. per litre). In the same way in summer frogs the uranium or the thorium content is to be diminished (from 25 mgm. of uranium salt to 5 mgm. and from 50 mgm. thorium salt to 10 mgm. per litre).[4]

The foregoing renders it more and more probable that the beneficial influence of potassiun in Ringer's circulating fluid is due to the radio-activity of the element. Positive certainty may be obtained through mesothorium- and radium-radiation.

Together with C. E. Benjamins and T. P. Feenstra (17), I made initially thirty-four experiments, afterwards a larger number, in which the Kroneckered frog's heart was exposed to a short-distance radiation. The heart had beforehand been deprived of its diffusible potassium by allowing a potassium-free fluid to run through it until a standstill

[4] S. de Boer will publish these experiments more fully.

ensued. This precaution is essential for if the diffusible potassium is not removed at all or only in part by employing a fluid whose salts are contaminated with potassium or a fluid, originally free of potassium, that has been contained in phials of common glass, which gives off potassium, the radiation is ineffectual. As the conditions are arranged well, however, the otherwise irrecoverably motionless heart is seen to recover its contractility abruptly, forcibly and regularly after half an hour's radiation when, as was done by us, 3 mgm., 5 mgm. or 6 mgm. of radium, respectively, mesothoruim is applied. The radiation-times for the various cases depend entirely on the past history of the organ (natural frequency of the pulsations; velocity of circulation; the tonus, in consequence of which the lacunae are more or less open; the time required by the heart to stop its beats through deprivation of diffusible potassium, etc.). The duration of the renewed, perfectly normal rhythm is also varying. A prolonged radiation generally evolves a secondary standstill.

It will be understood that during the experiment the circulation with potassium-free Ringer's solution goes on unintermittently. Jannink (18) found that in those cases about 1 mgm. of potassium per litre from the heart is added to the circulating fluid. In some degree a continual mobilization, therefore, takes place of the potassium from the solid form in which it occurs in the muscle[5] to the diffusible form. There is no appreciable difference in this respect between winter and summer frogs. In either case the outflowing liquid hardly contains any potassium when at the inflow it was potassium-free.

When recovery has been effected through radiation, it is not difficult to render visible "the second paradox" that we encountered in the course of our experiments. It consists in the arrest of the cardiac action directly when, instead of potassium-free mixture, the original Ringer's solution has been administered. During the initial pulsations this paradoxical phenomenon is still absent, but after about twenty or thirty pulsations it is sure to make its appearance. After the fluid, free from potassium, is allowed to run through, the heart recovers itself. This induced us to believe that the normal amount of potassium, suddenly entering the heart-cells, evolves in it a quantum of radio-activity that, together with the electricity already accumulated through radiation, increases to an extent that is incompatible with a normal automaticity. For the same reason the standstill in diastole occurs

[5] The *permanent* radiation of the non-diffusible potassium, present in the muscle, does not seem to exert a noticeable influence.

which is familiar to us from potassium-intoxication. The reaction is reversible. Circulation with potassium-free Ringer's solution restores the beats rather soon.

In this connection it is a question of vital importance to know the quanta of radio-activity concerned in such cases. A certain quantum most likely causes contractility. Maybe double that quantity proves to be too much. The adequate quantum can no doubt be computed from the circulation experiments with Ringer's mixture to which is added 5 micromgm. of radium-salt so that per litre and per second 41×10^{-4} erg is sent through. However, at the most only 0.0001 litre passes per second. Then the quantum of energy that causes recovery is at any rate less than 4×10^{-7} erg. With this we approach the energy quanta capable of stimulating our senses close to the threshold. Thus the result of this calculation does not seem to be improbable (19).

The results of the experiments with potassium-uranium mixtures, reported above, have induced me to study the behavior of uranium hearts toward radiation. They cannot stand radiation. After a short interval the rhythm ceases to return again after the removal of radium (or mesothorium). Such experiments succeed best when starting from a potassium-uranium equilibrium, i.e., a condition in which the heart does not beat because it is fed with a Ringer-solution that contains antagonistic amounts of potassium and uranium. We took per litre 40 mgm. of potassium chlorid and 10 mgm. of uranylnitrate (inclusive of the water of crystallization) in the hearts of winter frogs; and 30 to 50 mgm. of potassium chlorid and 5 mgm. of uranylnitrate in the hearts of summer frogs. A heart in a state of complete quiescence and relaxation, fed with such a solution for some time, say five minutes, will resume its beats in a comparatively short time when radium or mesothorium is brought close to it. Upon increasing the uranium-dosis in the fluid by slow degrees, the cardiac action is soon arrested again and will recommence once more on further uranium increment. So there is a radiation-uranium antagonism in the same sense as there is a potassium-uranium antagonism. Quantitative relations (20) may even be traced between the distances of the radium or the mesothorium and the amounts of uranium used to counteract them. No account is taken here of time relations, the gist of the matter being the distances and the uranium-quanta. Those distances are surprisingly small, all falling within 1 cm. Furthermore, the uranium-quantum, taken as a counterpoise, is considerably diminished by placing thin aluminium screens between mesothorium and heart. I inferred from these ex-

periments that the biological activity is due to the extremely weak β-rays shot out by the radium and the mesothorium.

In the radiation experiments just made mention of, in which radiation was contrasted with the uranium administered internally, we have encountered a third paradox. A prolonged experiment, in which an overbalance of radiation or of uranium has alternately been acting on the heart, evokes a paradox different from the two paradoxes we have hitherto met. The heart will ultimately stand still as well with a normal Ringer's solution as with that containing uranium, and nevertheless pulsate with a potassium-free circulating fluid. In a number of such cases this paradoxical behavior has been overcome by an excessively large uranium-dosis.

SUMMARY

In summarizing the above we arrive at the conclusion both simple and startling that, provided that only radio-active quanta be taken, all radio-active elements administered to the isolated heart internally are capable of sustaining the automaticity. So is also radiation, with the understanding that it is applied in a certain dosage. In some of these cases α-rays come into play, in others β-rays. Both are active, but when acting in conjunction they counterbalance each other. Obviously it is the electric charge, imparted by the α- and β-particles, to which the results are to be ascribed. Whether the γ-rays also come into operation I dare not decide.

Recently also a screen-effect of the diffusible potassium has shown itself. Excess of radiation is detrimental to the heart that is free from potassium, but harmless for a heart that has been fed with normal Ringer's solution. The non-diffusible potassium of the heart muscle is wanting in a screen-effect. It seems to have in our sense no perceptible working at all.

The hypothesis that the significance of radio-activity for the automaticity of the heart rests on the application of an electric charge has occasioned a number of new experiments. They have brought to light that a galvanic current arrests a beating uranium heart suddenly and temporarily, leaving it in a state of utter relaxation, and that in such a uranium heart extrasystoles can be generated only by mechanical stimuli (not by induced electrical). We meet, however, with many theoretical difficulties. So aequiradio-activity is equivalency of energy, but electrical charge is a factor of quantity in energy. The dimensions are not the same.

It has also been proved that the effect of radio-activity, in the case described above, is decisive not only for the automaticity of the heart but also for a number of other functions. In my laboratory this has been established for the vascular endothelium (21), for the irritability of the muscle, directly and indirectly (22), recently for the intestinal movements (with a reservation though), for the regulating functions of the extracardiac nerves (23), and in the laboratory of Hamburger (24) for the glomerulus-epithelium.

The results described induced me to project a provisory working-hypothesis, which was communicated by me on the Congress of Dutch Physiologists in Amsterdam, December, 1916. It served me and my coworkers for guidance and is given a brief exposition in Ned. Tijdschr. voor Geneeskunde, 1917, i, 1178.

BIBLIOGRAPHY

(1) CAMPBELL AND WOOD: Proc. Cambridge Phil. Soc., 1906–08, xiv, 15.
(2) LAZARUS: Handbuch der Radiumbiologie und Therapie, 264.
(3) RUTHERFORD: Marx, Handbuch der Radiologie, ii, 522.
(4) RUTHERFORD: Marx, Handbuch der Radiologie, ii, 422.
(5) BÜCHNER: K. Akad. v. Wetensch., Amsterdam, xviii, 91.
(6) LAZARUS: Handbuch der Radiumbiologie und Therapie.
(7) RINGER: Journ. Physiol., iv, 370.
(8) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, xxiv, 1812; 1916, xxv, 37.
(9) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, 1916, xxv, 520.
(10) HOWELL AND DUKE: This Journal, 1908, xxi, 51.
(11) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, 1917, xxv, 1096.
(12) ZWAARDEMAKER: Dutch Congress for Phys. and Med. Sciences, The Hague, April 14, 1917.
(13) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, 1917.
(14) LOEB AND CATTELL: Journ. Biol. Chem., 1915, xxiii, 41.
(15) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, 1917, xxv, 1101.
(16) JOLLES: Thesis, Utrecht, 1917.
(17) ZWAARDEMAKER, BENJAMINS AND FEENSTRA: Ned. Tijdschr. v. Geneesk., 1916, ii, 1923.
(18) JANNINK: Congress of Dutch Phsyiologists, Amsterdam, 1916.
(19) ZWAARDEMAKER: K. Akad. v. Wetensch., 1917, xxv, 1098.
(20) ZWAARDEMAKER: K. Akad. v. Wetensch., Amsterdam, 1917, xxv, 1282.
(21) GUNZBURG: Congress of Dutch Physiologists, Amsterdam, 1916.
(22) GUNZBURG: Dutch Congress for Phys. and Med. Sciences, The Hague, April, 1917.
(23) ZWAARDEMAKER AND LELY: Arch. Néerland. Physiol., 1917, i, 745.
(24) HAMBURGER AND BRINKMAN: K. Akad. v. Wetensch., Amsterdam, 1917, xxv, 944.